10/022,276 12-26-06 DAC #

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 6,569,837	Attorney Docket No.: 06171.105080 (IDX 1000 CON)
Issued:	May 27, 2003	
Inventors:	Gilles Gosselin, *et al.*	
Assignee:	Idenix Pharmaceuticals, Inc. *et al.*	
For:	β-L-2′-Deoxy Pyrimidine Nucleosides for the Treatment of Hepatitis B	

MAIL STOP PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR THE EXTENSION OF THE TERM OF THE UNITED STATES PATENT NO. 6,569,837 UNDER 35 U.S.C. § 156

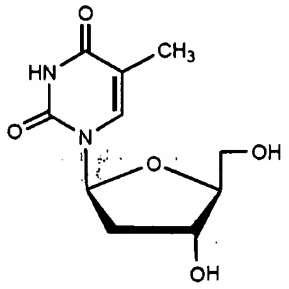
Sir:

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Idenix Pharmaceuticals, Inc., Centre National de La Recherche Scientifique, and L'Universite Montpellier II through the undersigned, represent that they are the co-owners of record of United States Patent No. 6,569,837 ("the '837 patent"), attached hereto as Exhibit A, and hereby request an extension of the patent term thereof. Copies of the assignments and assignment recordations from the '837 patent and from U.S. Patent No. 6,395,716 (the parent of the '837 patent), which were recorded at Reel 010271, frame 0725, at Reel 012937, frame 0346, at Reel 013193, frame 0841, and at Reel 013718, frame 0543 confirming that all right, title, and interest resides in Idenix Pharmaceuticals, Inc., Centre National de La Recherche Scientifique, and L'Universite Montpellier II are attached hereto as Exhibit B.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics."

The approved product is sold under the trade name TYZEKA®, the active ingredient of which is telbivudine. A chemical name of telbivudine is 1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl-1H pyrimidine-2,4-dione, and the structure is shown below:



Synonyms for telbivudine include "SEBIVO,"[1] "β-L-thymidine," "β-L-2'-deoxythymidine," "2'-deoxy-β-L-thymidine," "β-LdT" and "LdT." The molecular weight of telbivudine is 242.23 g/mol, and its empirical formula is $C_{10}H_{14}N_2O_5$. (*See* Product Label at Exhibit C, page 8).

As currently approved, the product sold under the trade name TYZEKA® is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease. (*See* Product Label, page 13). Currently, the approved product is available in the form of a 600 mg film-coated tablet for oral administration. (*See* Product Label at Exhibit C, page 9).

(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred."

The product sold under the trade name TYZEKA® (telbivudine) was subject to regulatory review for an investigational new drug application ("IND") and a new drug application ("NDA") under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 ("FFDCA").

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[1] This was the preliminary name for TYZEKA®.

Section 505(b) of the FFDCA, 21 U.S.C. §355(b), authorizes the filing of an NDA for a new drug. The Food and Drug Administration ("FDA") subsequently approved the product NDA (22-011) under the authority granted by section 505(c) of the FFDCA, 21 U.S.C. § 355(c).

(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred."

The product sold under the trade name TYZEKA® received permission for commercial marketing or use by the FDA pursuant to section 505(b) of the FFDCA, 21 U.S.C. § 355(b), on October 25, 2006. Copies of the Product Label and FDA Approval Letter are attached as Exhibits C and D, respectively.

(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum- Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."

The active ingredient in the product sold under the trade name TYZEKA® is telbivudine. Telbivudine has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted."

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being December 22, 2006.

(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."

The complete identification of the patent for which extension is sought is as follows:

Inventors:	Gilles Gosselin, Jean-Louis Imbach and Martin L. Bryant
Patent No.:	6,569,837
Issue Date:	May 27, 2003
Expiration Date:	August 10, 2019

(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."

A copy of U.S. Patent No. 6,569,837 ("the '837 patent"), for which this extension is sought, is attached hereto as Exhibit A.

(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."

A copy of the terminal disclaimer mailed July 17, 2002 and received at the United States Patent and Trademark Office on July 23, 2002, which disclaims the terminal part of the '837 patent extending beyond the expiration of U.S. Patent Nos. 6,395,716, 6,444,652 (application no. 09/459,150) and 6,566,344 (application no. 10/022,148), is attached hereto as Exhibit E.

No reexamination certificate for the '837 patent was issued.

A copy of the 4th year maintenance fee receipt is attached hereto as Exhibit F; thus, no maintenance fee is currently due. The 8th year maintenance fee is not due until 2011.

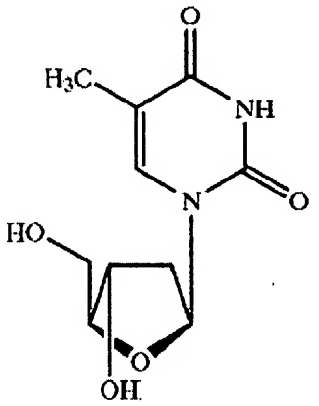
(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product;
(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and
(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product."

The '837 patent claims, *inter alia*, a method of using the approved product, *e.g.* a method of using the active ingredient of the product sold under the trade name TYZEKA®. More specifically, at least independent claim 14 of the '837 patent, and at least dependent claims 29-31

and 37-39, claim methods of using the active ingredient of the approved product. Claim 14 is set forth below:

Claim 14

> A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-thymidine of the formula:



> or pharmaceutically acceptable salt thereof.

The Product Label states that the approved product is indicated for the treatment of chronic hepatitis B in adult patients. (*See* Product Label at Exhibit C, page 13). The Product Label also indicates that, in clinical trials, administration of the product resulted in suppression of hepatitis B virus DNA in patients having hepatitis B virus infection. (*See* Product Label at Exhibit C, pages 12-14). The formula of claim 14 depicts the same compound that is depicted by formula and identified by chemical name in the Product Label. (*See* Product Label at Exhibit C, page 8). Although claim 14 and the Product Label depict the compound from different orientations, the depicted compounds are identical. Thus, claim 14 claims methods of using the approved product.

Dependent claim 29 claims the method of claim 14 wherein the β-L-thymidine is at least 95% in its designated enantiomeric form. The β-L-thymidine of the product sold under the trade name TYZEKA® is at least 95% in its designated enantiomeric form.

Dependent claim 30 claims the method of claim 14, wherein the β-L-thymidine is administered in a pharmaceutically acceptable carrier, and dependent claim 31 claims the method of claim 29 wherein the pharmaceutically acceptable carrier is suitable for oral delivery. The

Product Label states that the approved product is supplied in film-coated tablets. (*See* Product Label, page 23). The tablets contain inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate, and the tablet coating contains titanium dioxide, polyethylene glycol, talc and hypromellose. (*See* Product Label, page 22). According to the '837 patent, pharmaceutically acceptable carriers include, but are not limited to, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and polyethylene glycol. (*See* '837 patent at col. 39, line 45, through col. 41, line 18). The Product Label for the approved product states that the film-coated tablets are available for oral administration. (*See* Product Label, page 23). Since the product sold under the trade name TYZEKA® is supplied in a pharmaceutically acceptable carrier suitable for oral delivery, dependent claims 30 and 31 claim methods of using the approved product.

Dependent claim 37 claims the method of claim 29 wherein the compound is in the form of a dosage unit. Dependent claim 38 claims the method of claim 37, wherein the dosage unit contains 10 to 1500 mg of the compound, and dependent claim 39 claims the method of claim 37 or 38, wherein the dosage unit is a tablet or capsule. The Product Label states that the approved product is supplied as a 600 mg tablet. (*See* Product Label, page 23). The recommended dose of the product for chronic hepatitis B patients is 600 mg once daily. (*See* Product Label, page 22). Since the product sold under the trade name TYZEKA® is supplied in a dosage unit that is a tablet containing 600 mg of the compound, dependent claims 37-39 claim methods of using the approved product.

Thus, at least dependent claims 29-31 and 37-39 also claim methods of using the approved product.

(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

> ***(i) For a patent claiming a human drug, antibiotic, or human biological product:***
> ***(A) The effective date of the investigational new drug (IND) application and the IND number;***
> ***(B) The date on which a new drug application (NDA) or a Produce License Application (PLA) was initially submitted and the NDA or PLA number; and***
> ***(C) The date on which the NDA was approved or the Product License issued."***

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for the product sold under the trade name TYZEKA® are as follows:

(a) Investigational new drug ("IND") application number 64,459 was received by the FDA on May 31, 2000 and became effective on July 1, 2000, which is 30 days after the receipt of the IND by the FDA. IND application number 64,459 was under a clinical hold until August 15, 2000. As shown in the Assignment documents, Novirio is a previous name of patent owner Idenix Pharmaceuticals, Inc.

(b) The new drug application ("NDA") was submitted on December 30, 2005, and was later assigned NDA number 22-011. The NDA for the approved product was initially submitted using the preliminary proprietary name SEBIVO; the name was later changed to TYZEKA®.

(c) NDA number 22-011 was approved by the FDA on October 25, 2006 (Exhibit D).

(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."

A chronology of selected regulatory activities is attached hereto as Exhibit G to briefly describe certain activities undertaken with respect to the approval of the product sold under the trade name TYZEKA® during the applicable regulatory review period and the dates applicable to such activities.

(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined."

Applicant is of the opinion that the '837 patent is eligible for an extension and estimates the extension to be **442 days**, the calculation of which is described below.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '837 patent claims a method of using the active ingredient;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '837 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '837 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owners of record of the '837 patent;

(e) Pursuant to 35 U.S.C. § 156(a)(4), the approved product, sold under the trade name TYZEKA®, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. § 156(a)(5), the permission for the commercial marketing or use of the product sold under the trade name TYZEKA® after the regulatory review period is the first permitted commercial marketing or use of this product;

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product sold under the trade name TYZEKA®.

B. Regulatory Review Period:

(a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from July 1, 2000 (the date IND application number 64,459 became effective) to December 30, 2005 (the date the NDA was initially submitted) is 2,008 days. Accordingly, Applicant calculates the "Testing Phase" as

2,008 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from December 30, 2005 (the date the NDA was initially submitted) to October 25, 2006 (the date of NDA approval) is 299 days. Accordingly, Applicant calculates the "Approval Phase" as 299 days.

C. Extended Patent Term:

(a) The number of days in the regulatory review period which were on and before May 27, 2003, the date on which the '837 patent issued, is 1,060 days. Accordingly, 1,060 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the "Adjusted Testing Phase" to be 948 days (2,008 days minus 1,060 days).

(b) As demonstrated in Exhibit G, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 474 days. Accordingly, 474 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii). After the above adjustments, the total remaining Testing Phase and Approval Phase is 773 days (474 days plus 299 days).

(d) The period remaining in the term of the patent (set to expire August 10, 2019) measured from the date of approval of the product sold under the trade name TYZEKA® (October 25, 2006) (4,672 days) when added to the period of extension (773 days) is 5,445 days, which is more than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) should operate to reduce the regulatory review period. Pursuant to 37 C.F.R. § 1.775(d)(2)-(4) the period for extension should end October 25, 2020, or fourteen years (5,114 days) from the date of approval of the product sold under the trade name TYZEKA® (October 25, 2006). Accordingly, the period of extension should be **442** days (5,114 days minus 4,672 days).

(e) The period of extension (442 days) is less than five (5) years.

Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

Applicants note that they are cofiling today an APPLICATION FOR THE EXTENSION OF THE TERM OF THE UNITED STATES PATENT NO. 6,395,716 UNDER 35 U.S.C. § 156 with the understanding the Applicants will select only one patent for term extension before a patent term extension is granted.

(14) "The prescribed fee for receiving and acting upon the application for extension."

The prescribed fee for receiving and acting upon this application is believed to be $1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). A Credit Card Payment form authorizing the Commissioner to charge the $1,120.00 fee is enclosed. The Commissioner is authorized to charge this fee and any additional required fees, or credit any overpayment, to Deposit Account No. 11-0980.

(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."

Please direct all inquiries and correspondence relating to this application to:

James D. Johnson, Ph.D., Registration No. 31,771
KING & SPALDING LLP
1180 Peachtree Street, 34th Floor
Atlanta, GA 30309

The name and telephone number of the person to whom inquiries may be made, at the above address, is:

James D. Johnson, Ph.D.
Telephone: 404-572-2529
Fax: 404-572-5134

A power of attorney is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 20786.

(16) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)."

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicants hereby states that these copies are accurate and true duplicates of the original.

Respectfully submitted,

Date: December 21, 2006

James Dean Johnson, Ph.D. 31,771 (Reg. No.)

Robert E. Richards 29,125 (Reg. No.)

EXPRESS MAIL NO. **EV 863735892 US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 6,569,837	Attorney Docket No.: 06171.105080 (IDX 1000 CON)
Issued:	May 27, 2003	
Inventors:	Gilles Gosselin, *et al.*	
Assignee:	Idenix Pharmaceuticals, Inc. *et al.*	
For:	β-L-2′-Deoxy Pyrimidine Nucleosides for the Treatment of Hepatitis B	

MAIL STOP PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FEE TRANSMITTAL LETTER
FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156

Sir:

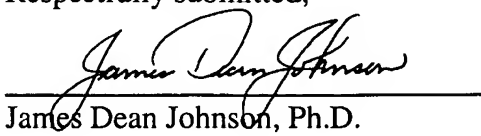
Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 6,569,837 accompanied by two additional copies. The undersigned attorney for Applicants hereby state that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

Exhibit A	U.S. Patent No. 6,569,837
Exhibit B	Assignment Recordations & Assignments
Exhibit C	Approved Product Label
Exhibit D	FDA Approval Letter
Exhibit E	Terminal Disclaimer
Exhibit F	Maintenance Fee Payment Record
Exhibit G	Compendium of Certain Regulatory Activities in Connection with the product sold under the trade name TYZEKA® IND and NDA

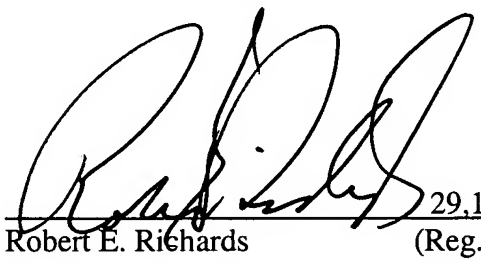
Enclosed is a Credit Card Authorization Form authorizing the Commissioner to charge the fee estimated to be $1,120.00. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 11-0980.

Respectfully submitted,

Date: December 21, 2006



31,771
James Dean Johnson, Ph.D. (Reg. No.)



29,125
Robert E. Richards (Reg. No.)

Express Mail No. **EV 863735892 US**

APPLICATION FOR THE EXTENSION OF THE TERM OF THE UNITED STATES PATENT NO. 6,569,837 UNDER 35 U.S.C. § 156

Certificate of Express Mailing under 37 CFR 1.10

I hereby certify that the below-listed correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated below and is addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Deposit Date: December 21, 2006

Docket No.: 06171.105005 (IDX 1000 CON)

Express Mail Label No.: **EV 863735892 US**

Enclosures (in triplicate): Application for Patent Term Extension (13 pgs.); Fee Transmittal Letter for an Application for Extension under 35 U.S.C. § 156 (2 pgs.); Exhibit A U.S. Patent No. 6,569,837 (32 pgs.) ; Exhibit B Assignment Recordations & Assignments (39 pgs); Exhibit C Approved Product Label (21 pgs.); Exhibit D FDA Approval Letter (7 pgs.); Exhibit E Terminal Disclaimer (2 pgs.); Exhibit F Maintenance Fee Payment Record (1 pgs.); Exhibit G Compendium of Certain Regulatory Activities in Connection with the product sold under the trade name TYZEKA® IND and NDA (35 pgs.); Revocation and Grant of Power of Attorney (9 pgs.); Credit Card Payment Form (1 pg.) and Return Receipt Postcard.

John Ezcurra

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
GOSSELIN ET AL.	)	
	)	Art Unit: **1623**
Application No. **10/022,276**		
Patent No. **6,569,837**	)	
	)	Examiner: **Lawrence E. Crane**
Filed: **December 14, 2001**	)	
	)	Attorney Docket No. **06171.105080**
For: **β-L-2'-DEOXY NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B**	)	**(IDX 1000 CON 1)**

REVOCATION AND GRANT OF POWER OF ATTORNEY; CHANGE OF CORRESPONDENCE ADDRESS; AND STATEMENT UNDER 37 CFR 3.73(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Revocation/Grant of Power of Attorney

Idenix Pharmaceuticals, Inc., Centre National De La Recherche Scientifique and L'Universite Montpellier II, joint owners by assignment of all right, title, and interest in and to the subject application, hereby revoke all powers of attorney heretofore granted for the above-identified application and hereby appoints the practitioners associated with **Customer Number 20786** as the attorneys of record herein, with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

Change of Correspondence Address

Please direct all future correspondence in the application to James Dean Johnson, Ph.D., at the address associated with the customer number provided above.

Statement Under 37 CFR 3.73(b)

Assignees, Idenix Pharmaceuticals, Inc., a corporation of the State of Delaware, having a place of business at 60 Hampshire Street, Cambridge, MA 02139; Centre National De la Recherche Scientifique, having a place of business at 3, rue Michel-Ange, F-75794 Paris Cedex 16, France ; and L'Universite Montpellier II, having a place of business at 2 Place Eugene Bataillon 34095, Montpellier Cedex 5, France certify that they are the assignees of the entire right, title, and interest in the above-identified patent application by virtue of a chain of title from the respective inventors of the subject matter disclosed and claimed therein. The chain of title is as set forth below.

Gilles Gosselin and Jean-Louis Imbach assigned their interest in the invention to Centre National De La Recherche Scientifique (CNRS) in U.S. Patent Application No. 09/371,747. The assignment was recorded in the United States Patent and Trademark Office on September 27, 1999, at Reel 010271, Frame 0725. Martin L. Bryant assigned his interest in the invention to Novirio Pharmaceuticals Limited in U.S. Patent Application No. 09/371,747. The assignment was recorded in the United States Patent and Trademark Office on September 27, 1999, at Reel 010271, Frame 0725. CNRS assigned a portion of its interest in the application to L'Universite Montpellier II in an assignment recorded in U.S. Patent Application No. 10/022,276 on June 3, 2002 at reel 012937, frame 0346. The change of name from Novirio Pharmaceuticals Limited to Idenix Pharmaceuticals Inc. was recorded in the United States Patent and Trademark Office on August 19, 2002, at Reel 013193, Frame 0841.

The undersigned is empowered to sign this Revocation and Grant of Power of Attorney on behalf of the Assignee.

Idenix Pharmaceuticals, Inc.

Date: Dec. 18, 2006

By: _____

Name: JP Sommadossi

Title: Chairman + CEO

Centre National De La Recherche Scientifique

Date: _____

By: _____

Name: _____

Title: _____

L'Universite Montpellier II

Date: _____

By: _____

Name: _____

Title: _____

DI85236-02

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

GOSSELIN ET AL.

Application No. **10/022,276**

Patent No. **6,569,837**

Filed: **December 14, 2001**

For: **β-L-2'-DEOXY NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B**

Art Unit: **1623**

Examiner: **Lawrence E. Crane**

Attorney Docket No. **06171.105080**
(IDX 1000 CON 1)

REVOCATION AND GRANT OF POWER OF ATTORNEY; CHANGE OF CORRESPONDENCE ADDRESS; AND STATEMENT UNDER 37 CFR 3.73(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Revocation/Grant of Power of Attorney

Idenix Pharmaceuticals, Inc., Centre National De La Recherche Scientifique and L'Universite Montpellier II, joint owners by assignment of all right, title, and interest in and to the subject application, hereby revoke all powers of attorney heretofore granted for the above-identified application and hereby appoints the practitioners associated with **Customer Number 20786** as the attorneys of record herein, with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

Change of Correspondence Address

Please direct all future correspondence in the application to James Dean Johnson, Ph.D., at the address associated with the customer number provided above.

Statement Under 37 CFR 3.73(b)

Assignees, Idenix Pharmaceuticals, Inc., a corporation of the State of Delaware, having a place of business at 60 Hampshire Street, Cambridge, MA 02139; Centre National De la Recherche Scientifique, having a place of business at 3, rue Michel-Ange, F-75794 Paris Cedex 16, France ; and L'Universite Montpellier II, having a place of business at 2 Place Eugene Bataillon 34095, Montpellier Cedex 5, France certify that they are the assignees of the entire right, title, and interest in the above-identified patent application by virtue of a chain of title from the respective inventors of the subject matter disclosed and claimed therein. The chain of title is as set forth below.

Gilles Gosselin and Jean-Louis Imbach assigned their interest in the invention to Centre National De La Recherche Scientifique (CNRS) in U.S. Patent Application No. 09/371,747. The assignment was recorded in the United States Patent and Trademark Office on September 27, 1999, at Reel 010271, Frame 0725. Martin L. Bryant assigned his interest in the invention to Novirio Pharmaceuticals Limited in U.S. Patent Application No. 09/371,747. The assignment was recorded in the United States Patent and Trademark Office on September 27, 1999, at Reel 010271, Frame 0725. CNRS assigned a portion of its interest in the application to L'Universite Montpellier II in an assignment recorded in U.S. Patent Application No. 10/022,276 on June 3, 2002 at reel 012937, frame 0346. The change of name from Novirio Pharmaceuticals Limited to Idenix Pharmaceuticals Inc. was recorded in the United States Patent and Trademark Office on August 19, 2002, at Reel 013193, Frame 0841.

The undersigned is empowered to sign this Revocation and Grant of Power of Attorney on behalf of the Assignee.

Idenix Pharmaceuticals, Inc.

Date: _____ By: _____

Name: _____

Title: _____

Centre National De La Recherche Scientifique

Date: _____ By: Directeur de la Politique Industrielle

Name: ~~Marc J. LEDOUX~~

Title: _____

L'Universite Montpellier II

Date: _____ By: _____

Name: _____

Title: _____

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
GOSSELIN ET AL.	)	
	)	Art Unit: **1623**
Application No. **10/022,276**		
Patent No. **6,569,837**	)	
	)	Examiner: **Lawrence E. Crane**
Filed: **December 14, 2001**	)	
	)	Attorney Docket No. **06171.105080**
For: **β-L-2'-DEOXY NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B**	)	**(IDX 1000 CON 1)**

REVOCATION AND GRANT OF POWER OF ATTORNEY; CHANGE OF CORRESPONDENCE ADDRESS; AND STATEMENT UNDER 37 CFR 3.73(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Revocation/Grant of Power of Attorney

Idenix Pharmaceuticals, Inc., Centre National De La Recherche Scientifique and L'Universite Montpellier II, joint owners by assignment of all right, title, and interest in and to the subject application, hereby revoke all powers of attorney heretofore granted for the above-identified application and hereby appoints the practitioners associated with **Customer Number 20786** as the attorneys of record herein, with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

Change of Correspondence Address

Please direct all future correspondence in the application to James Dean Johnson, Ph.D., at the address associated with the customer number provided above.

Statement Under 37 CFR 3.73(b)

Assignees, Idenix Pharmaceuticals, Inc., a corporation of the State of Delaware, having a place of business at 60 Hampshire Street, Cambridge, MA 02139; Centre National De la Recherche Scientifique, having a place of business at 3, rue Michel-Ange, F-75794 Paris Cedex 16, France ; and L'Universite Montpellier II, having a place of business at 2 Place Eugene Bataillon 34095, Montpellier Cedex 5, France certify that they are the assignees of the entire right, title, and interest in the above-identified patent application by virtue of a chain of title from the respective inventors of the subject matter disclosed and claimed therein. The chain of title is as set forth below.

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The undersigned is empowered to sign this Revocation and Grant of Power of Attorney on behalf of the Assignee.

Idenix Pharmaceuticals, Inc.

Date: _____

By: _____

Name: _____

Title: _____

Centre National De La Recherche Scientifique

Date: _____

By: _____

Name: _____

Title: _____

L'Universite Montpellier II

Date: DECEMBER 18TH, 2006

By: _____

Name: JEAN-LOUIS CLAQ

Title: PRESIDENT.

Exhibit A

US006569837B1

(12) **United States Patent**
Gosselin et al.

(10) **Patent No.: US 6,569,837 B1**
(45) **Date of Patent: *May 27, 2003**

(54) **β-L-2'-DEOXY PYRIMIDINE NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B**

(75) Inventors: **Gilles Gosselin**, Montpellier (FR); **Jean-Louis Imbach**, Montpellier (FR); **Martin L. Bryant**, Carlisle, MA (US)

(73) Assignee: **Idenix Pharmaceuticals Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/022,276**

(22) Filed: **Dec. 14, 2001**

Related U.S. Application Data

(63) Continuation of application No. 09/371,747, filed on Aug. 8, 1999, now Pat. No. 6,395,716.
(60) Provisional application No. 60/096,110, filed on Aug. 10, 1998, and provisional application No. 60/131,352, filed on Apr. 28, 1999.

(51) **Int. Cl.**[7] **A61K 31/70**; C07H 19/073
(52) **U.S. Cl.** **514/45**; 514/46; 514/47; 514/48; 514/49; 514/50; 514/51; 536/28.5; 536/28.55
(58) **Field of Search** 514/45–51; 536/28.5, 536/28.55

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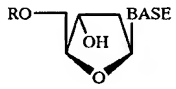
Primary Examiner—Johann Richter
Assistant Examiner—L Eric Crane
(74) *Attorney, Agent, or Firm*—King & Spalding L.L.P.; Sherry M. Knowles

(57) **ABSTRACT**

This invention is directed to a method for treating a host infected with hepatitis B comprising administering an effective amount of an anti-HBV biologically active 2'-deoxy-β-L-erythro-pentofuranonucleoside or a pharmaceutically acceptable salt or prodrug thereof, wherein the 2'-deoxy-β-L-erythro-pentofuranonucleoside has the formula:



wherein R is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base which may be optionally substituted. The 2'-deoxy-β-L-erythro-pentofuranonucleoside or a pharmaceutically acceptable salt or prodrug thereof may be administered either alone or in combination with another 2'-deoxy-β-L-erythro-pentofuranonucleoside or in combination with another anti-hepatitis B agent.

49 Claims, 4 Drawing Sheets

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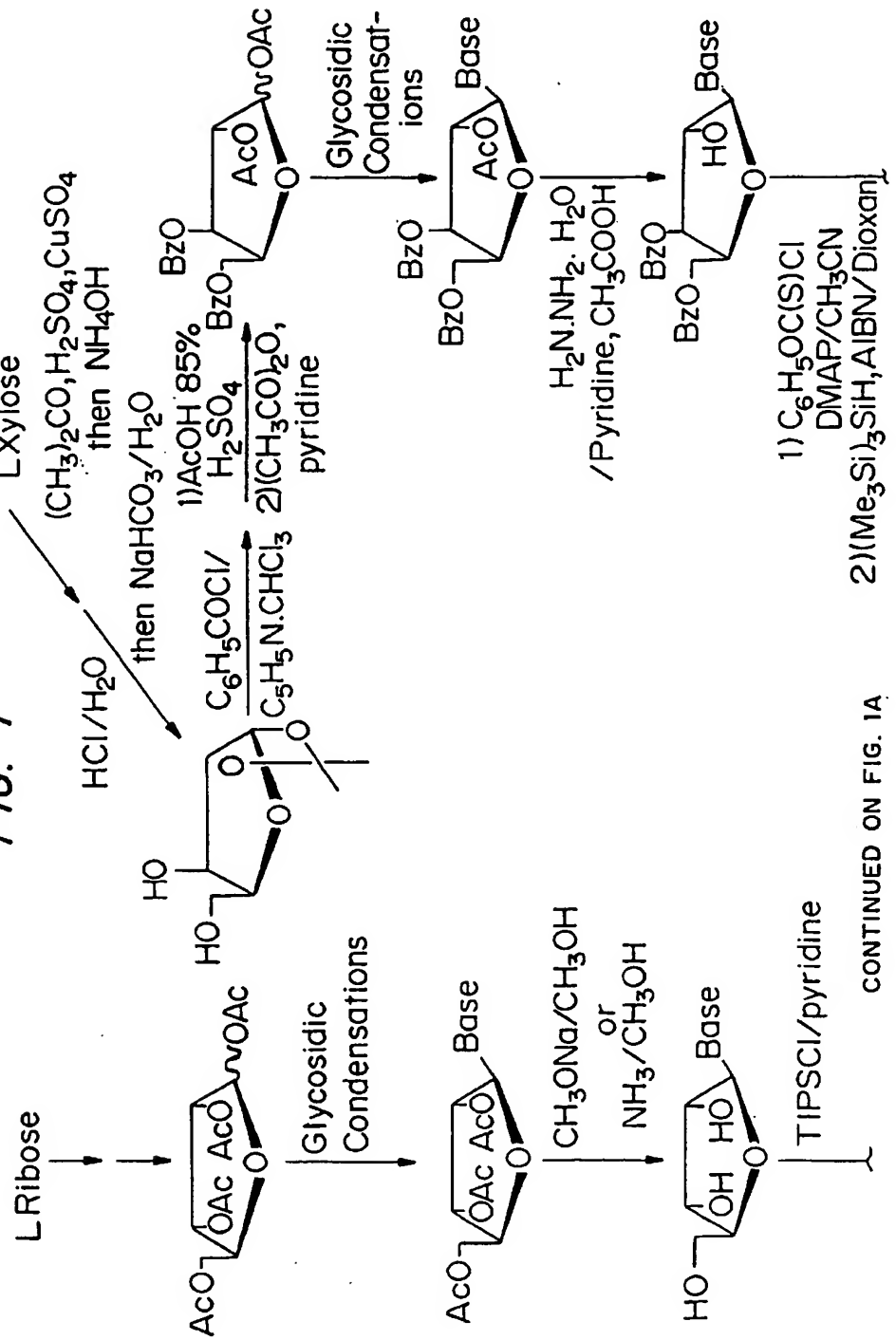
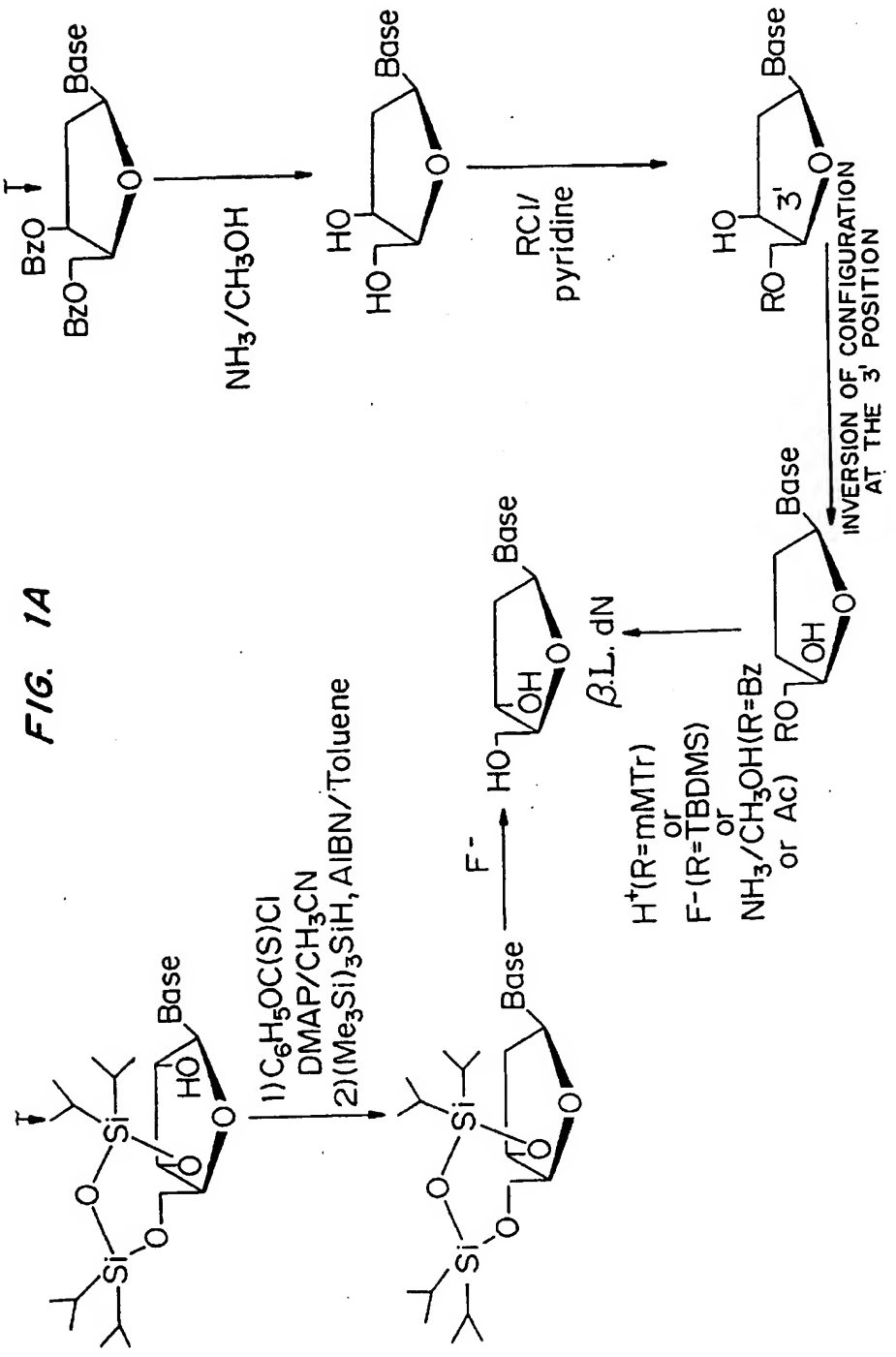
FIG. 1



CONTINUED ON FIG. 1A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BzO
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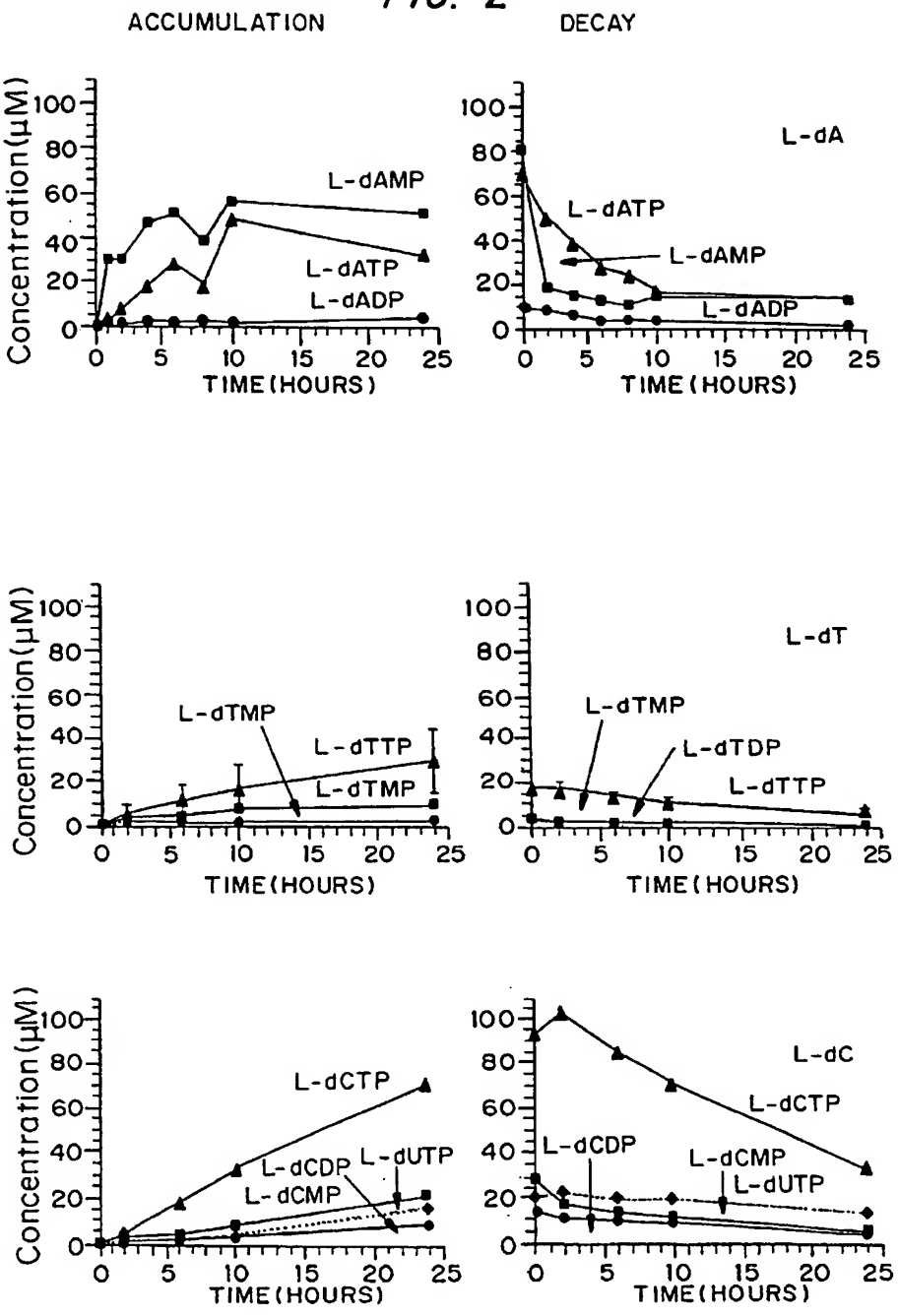
HO
HO
RCl/
pyridine
RO
3'
INVERSION OF CONFIGURATION
AT THE 3' POSITION
H^+(R=mMTr)
or
F-(R=TBDMS)
or
NH_3/CH_3OH(R=Bz
or Ac)
β.L. dN
F^-
1) $C_6H_5OC(S)Cl$
DMAP/CH_3CN
2) $(Me_3Si)_3SiH$, AIBN/Toluene
Si
O

FIG. 1A

FIG. 2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DECAY
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TIME(HOURS)
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L-dATP
L-dADP
L-dA
L-dTMP
L-dTTP
L-dTDP
L-dT
L-dCTP
L-dCDP
L-dUTP
L-dCMP
L-dC

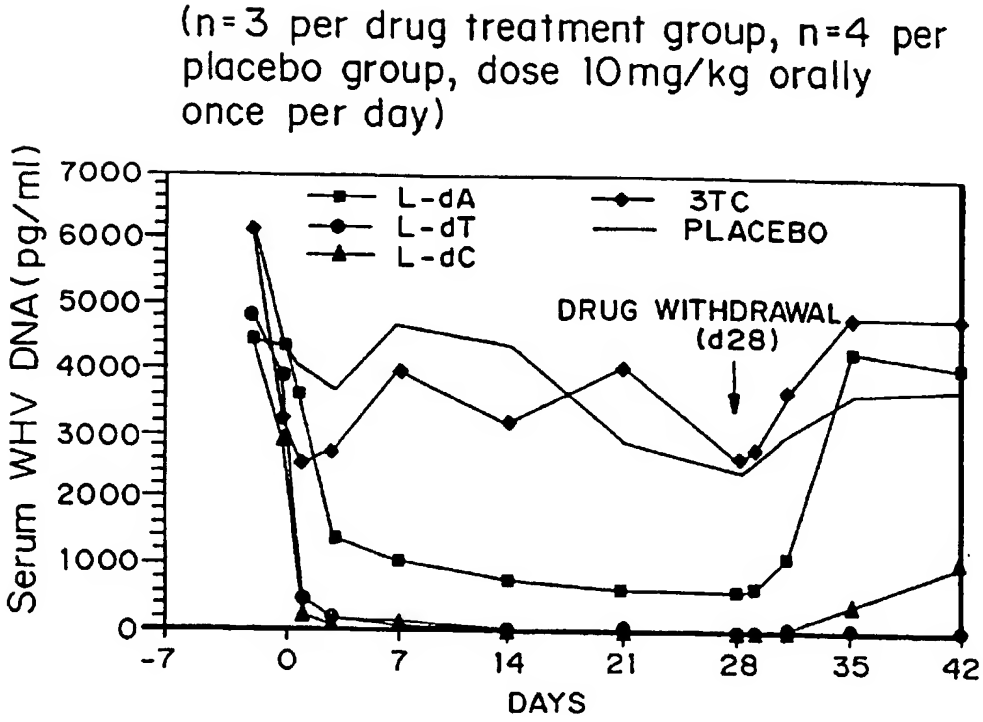

(n=3 per drug treatment group, n=4 per placebo group, dose 10mg/kg orally once per day)
Serum WHV DNA(pg/ml)
7000
6000
5000
4000
3000
2000
1000
0
L-dA
L-dT
L-dC
3TC
PLACEBO
DRUG WITHDRAWAL (d28)
-7
0
7
14
21
28
35
42
DAYS

FIG. 3

β-L-2'-DEOXY PYRIMIDINE NUCLEOSIDES FOR THE TREATMENT OF HEPATITIS B

This application is a continuation application of U.S. patent application Ser. No. 09/371,747 filed on Aug. 8, 1999, now U.S. Pat. No. 6,395,716, which claims priority to U.S. provisional application No. 60/096,110, filed on Aug. 10, 1998 and U.S. provisional application No. 60/131,352, filed on Apr. 28, 1999.

BACKGROUND OF THE INVENTION

This invention is in the area of methods for the treatment of hepatitis B virus (also referred to as "HBV") that includes administering to a host in need thereof, either alone or in combination, an effective amount of one or more of the active compounds disclosed herein, or a pharmaceutically acceptable prodrug or salt of one of these compounds.

HBV is second only to tobacco as a cause of human cancer. The mechanism by which HBV induces cancer is unknown, although it is postulated that it may directly trigger tumor development, or indirectly trigger tumor development through chronic inflammation, cirrhosis, and cell regeneration associated with the infection.

Hepatitis B virus has reached epidemic levels worldwide. After a two to six month incubation period in which the host is unaware of the infection, HBV infection can lead to acute hepatitis and liver damage, that causes abdominal pain, jaundice, and elevated blood levels of certain enzymes. HBV can cause fulminant hepatitis, a rapidly progressive, often fatal form of the disease in which massive sections of the liver are destroyed.

Patients typically recover from acute hepatitis. In some patients, however, high levels of viral antigen persist in the blood for an extended, or indefinite, period, causing a chronic infection. Chronic infections can lead to chronic persistent hepatitis. Patients infected with chronic persistent HBV are most common in developing countries. By mid-1991, there were approximately 225 million chronic carriers of HBV in Asia alone, and worldwide, almost 300 million carriers. Chronic persistent hepatitis can cause fatigue, cirrhosis of the liver, and hepatocellular carcinoma, a primary liver cancer.

In western industrialized countries, high risk groups for HBV infection include those in contact with HBV carriers or their blood samples. The epidemiology of HBV is very similar to that of acquired immune deficiency syndrome (AIDS), which accounts for why HBV infection is common among patients with AIDS or AIDS related complex. However, HBV is more contagious than HIV.

However, more recently, vaccines have also been produced through genetic engineering and are currently used widely. Unfortunately, vaccines cannot help those already infected with HBV. Daily treatments with α-interferon, a genetically engineered protein, has also shown promise, but this therapy is only successful in about one third of treated patients. Further, interferon cannot be given orally.

A number of synthetic nucleosides have been identified which exhibit activity against HBV. The (−)-enantiomer of BCH-189, known as 3TC, claimed in U.S. Pat. No. 5,539,116 to Liotta, et al., has been approved by the U.S. Food and Drug Administration for the treatment of hepatitis B. See also EPA 0 494 119 A1 filed by BioChem Pharma, Inc.

Cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane ("FTC") exhibits activity against HBV. See WO 92/15308; Furman, et al., "The Anti-Hepatitis B Virus

Activities, Cytotoxicities, and Anabolic Profiles of the (−) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-oxathiolane-5-yl]-Cytosine" *Antimicrobial Agents and Chemotherapy*, December 1992, page 2686–2692; and Cheng, et al., *Journal of Biological Chemistry*, Volume 267(20), 13938–13942 (1992).

von Janta-Lipinski et al. disclose the use of the L-enantiomers of 3'-fluoro-modified β-2'-deoxyribonucleoside 5'-triphosphates for the inhibition of hepatitis B polymerases (J. Med. Chem., 1998, 41,2040–2046). Specifically, the 5'-triphosphates of 3'-deoxy-3'-fluoro-β-L-thymidine (β-L-FTTP), 2',3'-dideoxy-3'-fluoro-β-L-cytidine (β-L-FdCTP), and 2',3'-dideoxy-3'-fluoro-β-L-5-methylcytidine (β-L-FMethCTP) were disclosed as effective inhibitors of HBV DNA polymerases.

WO 96/13512 to Genencor International, Inc. and Lipitek, Inc. discloses that certain L-ribofuranosyl nucleosides can be useful for the treatment of cancer and viruses. Specifically disclosed is the use of this class of compounds for the treatment of cancer and HIV.

U.S. Pat. No. Nos. 5,565,438, 5,567,688 and 5,587,362 (Chu, et al.) disclose the use of 2'-fluoro-5-methyl-β-L-arabinofuranolyluridine (L-FMAU) for the treatment of hepatitis B and Epstein Barr virus.

Yale University and University of Georgia Research Foundation, Inc. disclose the use of L-FddC (β-L-5-fluoro-2',3'-dideoxycytidine) for the treatment of hepatitis B virus in WO 92/18517.

The synthetic nucleosides β-L-2'-deoxycytidine (β-L-2'-dC), β-L-2'-deoxythymidine (β-L-dT) and β-L-2'-deoxyadenosine (β-L-2'-dA), are known in the art. Antonin Holy first disclosed β-L-dC and β-L-dT in 1972, "Nucleic Acid Components and Their Analogs. CLIII. Preparation of 2'-deoxy-L-Ribonucleosides of the Pyrimidine Series," *Collect. Czech. Chem. Commun.* (1972), 37(12), 4072–87. Morris S. Zedeck et al. first disclosed β-L-dA for the inhibition of the synthesis of induced enzymes in Pseudomonas testosteroni, *Mol. Phys.* (1967), 3(4), 386–95.

Certain 2'-deoxy-β-L-erythro-pentofuranonucleosides are known to have antineoplastic and selected antiviral activities. Verri et al. disclose the use of 2'-deoxy-β-L-erythro-pentofuranonucleosides as antineoplastic agents and as antiherpetic agents (*Mol. Pharmacol.* (1997), 51(1), 132–138 and *Biochem. J.* (1997), 328(1), 317–20). Saneyoshi et al. demonstrate the use of 2'-deoxy-L-ribonucleosides as reverse transcriptase (I) inhibitors for the control of retroviruses and for the treatment of AIDS, Jpn. Kokai Tokkyo Koho JP06293645 (1994).

Giovanni et al. tested 2'-deoxy-β-L-erythro-pentofuranonucleosides against partially pseudorabies virus (PRV), *Biochem. J.* (1993), 294(2), 381–5.

Chemotherapeutic uses of 2'-deoxy-β-L-erythro-pentofuranonucleosides were studied by Tyrsted et al. (*Biochim. Biophys. Acta* (1968), 155(2), 619–22) and Bloch, et al. (*J. Med. Chem.* (1967), 10(5), 908–12).

β-L-2'-deoxythymidine (β-L-dT) is known in the art to inhibit herpes simplex virus type 1 (HSV-1) thymidine kinase (TK). Iotti et al., WO 92/08727, teaches that β-L-dT selectively inhibits the phosphorylation of D-thymidine by HSV-1 TK, but not by human TK. Spaldari et al. reported that L-thymidine is phosphorylated by herpes simplex virus type 1 thymidine kinase and inhibits viral growth, *J. Med. Chem.* (1992), 35(22), 4214–20.

In light of the fact that hepatitis B virus has reached epidemic levels worldwide, and has severe and often tragic

effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat humans infected with the virus that have low toxicity to the host.

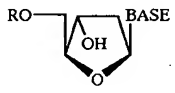
Therefore, it is an object of the present invention to provide new methods and compositions for the treatment of human patients or other hosts infected with hepatitis B virus.

SUMMARY OF THE INVENTION

A method for the treatment of hepatitis B infection in humans and other host animals is disclosed that includes administering an effective amount of a biologically active 2'-deoxy-β-L-erythro-pentofuranonucleoside (referred to alternatively herein as a β-L-d-nucleoside or a β-L-2'-d-nucleoside) or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination, optionally in a pharmaceutically acceptable carrier. The term 2'-deoxy, as used in this specification, refers to a nucleoside that has no substituent in the 2'-position.

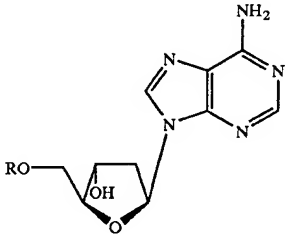
The disclosed 2'-deoxy-β-L-erythro-pentofuranonucleosides, or pharmaceutically acceptable prodrugs or salts or pharmaceutically acceptable formulations containing these compounds are useful in the prevention and treatment of hepatitis B infections and other related conditions such as anti-HBV antibody positive and HBV-positive conditions, chronic liver inflammation caused by HBV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. These compounds or formulations can also be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HBV antibody or HBV-antigen positive or who have been exposed to HBV.

In one embodiment of the present invention, the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative is a compournd of the formula:



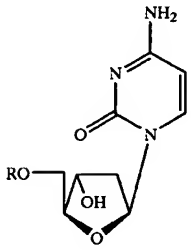
wherein R is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base which may optionally be substituted.

In another embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative is β-L-2'-deoxyadenosine or a pharmaceutically acceptable salt or prodrug thereof, of the formula:



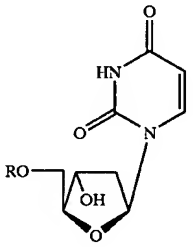
wherein R is H, mono, di or tri phosphate, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilized nucleotide prodrug).

In another embodiment, the 2'-deoxy-β-L-erythro-pentofiuranonucleoside derivative is β-L-2'-deoxycytidine or pharmaceutically acceptable salt or prodrug thereof of the formula:



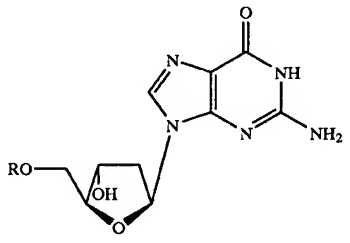
wherein R is H, mono, di or tri phosphate, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilzied nucleotide prodrug).

In another embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative is β-L-2'-deoxyuridine or pharmaceutically acceptable salt or prodrug thereof of the formula:



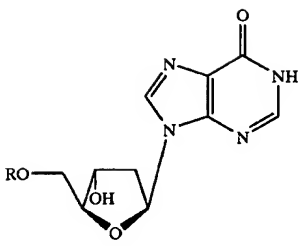
wherein R is H, mono, di or tri phosphate, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilzied nucleotide prodrug).

In another embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative is β-L-2'-deoxyguanosine or pharmaceutically acceptable salt or prodrug thereof of the formula:



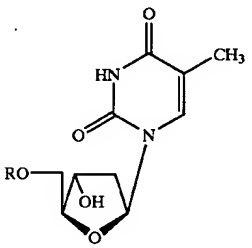
wherein R is H, mono, di or tri phosphate, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilized nucleotide prodrug).

In another embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative is β-L-2'-deoxyinosine or pharmaceutically acceptable salt or prodrug thereof of the formula:



wherein R is H, mono, di or tri phosphate, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilized nucleotide prodrug).

In another embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative is β-L-thymidine or a pharmaceutically acceptable salt or prodrug thereof of the formula:



wherein R is H, mono, di or tri phosphate, acyl, or alkyl, or a stabilized phosphate derivative (to form a stabilized nucleotide prodrug).

In another embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside is administered in alternation or combination with one or more other 2'-deoxy-β-L-erythro-pentofuranonucleosides or one or more other compounds which exhibit activity against hepatitis B virus. In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

In another embodiment, the invention includes a method for the treatment of humans infected with HBV that includes administering an HBV treatment amount of a prodrug of the disclosed 2'-deoxy-β-L-erythro-pentofuranonucleoside derivatives. A prodrug, as used herein, refers to a compound that is converted into the nucleoside on administration in vivo. Nonlimiting examples include pharmaceutically acceptable salt (alternatively referred to as "physiologically acceptable salts"), the 5'and N^4 (cytidine) or N^6 (adenosine) acylated or alkylated derivatives of the active compound, or the 5'-phospholipid or 5'-ether lipids of the active compound.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 illustrates a general process for obtaining β-L-erythro-pentafuranonucleosides (β-L-dN) using L-ribose or L-xylose as a starting material.

FIG. 2 is a graph which illustrates the metabolism of L-dA, L-dC, and L-dT in human Hep G2 cells in terms of accumulation and decay. The cells were incubated with 10 μM of compound.

FIG. 3 is a graph which illustrates the antiviral effect of β-L-dA, β-L-dT and β-L-dC in the woodchuck chronic hepatitis model.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "substantially in the form of a single isomer" or "in isolated form" refers to a 2'-deoxy-β-L-erythro-pentofuranonucleoside that is at least approximately 95% in the designated stereoconfiguration. In a preferred embodiment, the active compound is administered in at least this level of purity to the host in need of therapy.

As used herein, the term hepatitis B and related conditions refers to hepatitis B and related conditions such as anti-HBV antibody positive and HBV-positive conditions, chronic liver inflammation caused by HBV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. The method of the present invention includes the use of 2'-deoxy-β-L-erythro-pentofuranonucleoside derivatives prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HBV antibody or HBV-antigen positive or who have been exposed to HBV.

As used herein, the term alkyl, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon, typically of C_1 to C_{18}, preferably C_1 to C_6 and specifically includes but is not limited to methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, t-butyl, isopentyl, amyl, t-pentyl, cyclopentyl, and cyclohexyl.

As used herein, the term acyl refers to moiety of the formula —C(O)R', wherein R' is alkyl; aryl, alkaryl, aralkyl, heteroaromatic, alkoxyalkyl including methoxymethyl; aryalalkyl including benzyl; aryloxyalkyl such as phenoxymethyl; aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, or the residue of an amino acid. The term acyl specifically includes but is not limited to acetyl, propionyl, butyryl, pentanoyl, 3-methylbutyryl, hydrogen succinate, 3-chlorobenzoate, benzoyl, acetyl, pivaloyl, mesylate, propionyl, valeryl, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, and oleic.

As used herein, the term purine or pyrimidine base, includes, but is not limited to, N^6-alkylpurine and N^6-alkylpurines, N^6-acylpurines, N^6-benzylpurine, 6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-thioalkyl purine, N^2-alkylpurines, N^4-alkylpyrimidines, N^4-acylpyrimidines, 4-benzylpyrimidine, N^4-halopyrimidines, N^4-acetylenic pyrimidines, 4-acyl and N^4-acyl pyrimidines, 4-hydroxyalkyl pyrimidines, 4-thioalkyl pyrimidines, thymine, cytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-nitropyrimidine, C^5-aminopyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in

the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term biologically active nucleoside, as used herein, refers to a nucleoside which exhibits an EC_{50} of 15 micromolar or less when tested in 2.2.15 cells transfected with the hepatitis virion.

Preferred bases include cytosine, 5-fluorocytosine, 5-bromocytosine, 5-iodocytosine, uracil, 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-methyluracil, thymine, adenine, guanine, inosine, xanthine, 2,6-diaminopurine, 6-aminopurine, 6-chloropurine and 2,6-dichloropurine, 6-bromopurine, 2,6-dibromopurine, 6-iodopurine, 2,6-diiodopurine, 5-bromovinylcytosine, 5-bromovinyluracil, 5-bromoethenylcytosine, 5-bromoethenyluracil, 5-trifluoromethylcytosine, 5-trifluoromethyluracil.

The 2'-deoxy-β-L-erythro-pentofuranonucleoside can be provided as a 5' phospholipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L. S., N. Lyer, E. Leake, A. Raben, Modest E. J., D. L. W., and C. Piantadosi. 1990. Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation. AIDS Res Hum Retroviruses. 6:491–501; Piantadosi, C., J. Marasco C. J., S. L. morris-Natschke, K. L. Meyer, F. Gumus, J. R. Surles, K. S. Ishaq, L. S. Kucera, N. lyer, C. A. Wallen, S. Piantadosi, and E. J. Modest. 1991-Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity. J Med Chem. 34:1408–1414; Hostetler, K. Y., D. D. Richman, D. A. Carson, L. M. Stuhiniller, G. M. T. van Wijk, and H. van den Bosch. 1992. Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 31-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 31-deoxythymidine. Antimicrob Agents Chemother. 36:2025–2029; Hostetler, K. Y., L. M. Stuhmiller, H. B. Lenting, H. van den Bosch, and D. D. Richman. 1990. Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides. J. Biol Chem. 265:6112–7.

The 2'-deoxy-β-L-erythro-pentofuranonucleoside can be converted into a pharmaceutically acceptable ester by reaction with an appropriate esterifying agent, for example, an acid halide or anhydride. The nucleoside or its pharmaceutically acceptable prodrug can be converted into a pharmaceutically acceptable salt thereof in a conventional manner, for example, by treatment with an appropriate base or acid. The ester or salt can be converted into the parent nucleoside, for example, by hydrolysis.

As used herein, the term pharmaceutically acceptable salts or complexes refers to salts or complexes of the 2'-deoxy-β-L-erythro-pentofuranonucleosides that retain the desired biological activity of the parent compound and exhibit minimal, if any, undesired toxicological effects. Nonlimiting examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acids, naphthalenedisulfonic acids, and polygalacturonic acid; (b) base addition salts formned with cations such as sodium, potassium, zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with an organic cation formed from N,N-dibenzylethylene-diamine, ammonium, or ethylenediamine; or (c) combinations of (a) and (b); e.g., a zinc tannate salt or the like.

The term prodrug, as used herein, refers to a compound that is converted into the nucleoside on administration in vivo. Nonlimiting examples are pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), the 5' and N^4 or N^6 acylated or alkylated derivatives of the active compound, and the 5'-phospholipid and 5'-ether lipid derivatives of the active compound.

Modifications of the active compounds, specifically at the N^4, N^6 and 5'-O positions, can affect the bioavailability and rate of metabolism of the active species, thus providing control over the delivery of the active species.

A preferred embodiment of the present invention is a method for the treatment of HBV infections in humans or other host animals, that includes administering an effective amount of one or more of a 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative selected from the group consisting of β-L-2'-deoxyadenosine, β-L-2'-deoxycytidine, β-L-2'-deoxyuridine, β-L-2'-guanosine, β-L-2'-deoxyinosine, and β-L-2'-deoxythymidine, or a physiologically acceptable prodrug thereof, including a phosphate, 5' and or N^6 alkylated or acylated derivative, or a physiologically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess anti-HBV activity, or are metabolized to a compound or compounds that exhibit anti-HBV activity. In a preferred embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside is administered substantially in the form of a single isomer, i.e., at least approximately 95% in the designated stereoconfiguration.

Nucleotide Prodrugs

Any of the nucleosides described herein can be administered as a stabilized nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, *Antiviral Research*, 27 (1995) 1–17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

In one embodiment, the 2'-deoxy-β-L-erythro-pentofuranonucleoside is provided as 5'-hydroxyl lipophilic prodrug. Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 5'-OH position of the nucleoside or lipophilic preparations, include U.S. Pat. No. 5,149,794 (Sep. 22, 1992, Yatvin et al.); U.S. Pat. No. 5,194,654 (Mar. 16, 1993, Hostetler et al., U.S. Pat. No. 5,223,263 (Jun. 29, 1993, Hostetler et al.); U.S. Pat. No. 5,256,641 (Oct. 26, 1993, Yatvin et al.); U.S. Pat. No. 5,411,947 (May 2, 1995, Hostetler et al.); U.S. Pat. No. 5,463,092 (Oct. 31, 1995, Hostetler et al.); U.S. Pat. No. 5,543,389 (Aug. 6, 1996, Yatvin et al.); U.S. Pat. No. 5,543,390 (Aug. 6, 1996, Yatvin et al.); U.S. Pat. No. 5,543,391 (Aug. 6, 1996, Yatvin et al.); and U.S. Pat. No. 5,554,728 (Sep. 10, 1996; Basava et al.), all of which are incorporated herein by reference.

Foreign patent applications that disclose lipophilic substituents that can be attached to the 2'-deoxy-β-L-erythro-pentofuranonucleoside derivative of the present invention, or lipophilic preparations, include WO 89/02733, WO 90/00555, WO 91/16920, WO 91/18914, WO 93/00910, WO 94/26273, WO 96/15132, EP 0 350 287, EP 93917054.4, and WO 91/19721.

Additional nonlimiting examples of 2'-deoxy-β-L-erythro-pentofuranonucleosides are those that contain substituents as described in the following publications. These derivatized 2'-deoxy-β-L-erythro-pentofuranonucleosides can be used for the indications described in the text or otherwise as antiviral agents, including as anti-HBV agents. Ho, D. H. W. (1973) Distribution of kinase and deaminase of 1 β-D-arabinofuranosylcytosine in tissues of man and mouse. *Cancer Res.* 33, 2816–2820; Holy, A. (1993) Isopolar phosphorous-modified nucleotide analogues. In: De Clercq (Ed.), Advances in Antiviral Drug Design, Vol. I, JAI Press, pp. 179–231; Hong, C. I., Nechaev, A., and West, C. R. (1979a) Synthesis and antitumor activity of 1□-D-arabinofuranosylcytosine conjugates of cortisol and cortisone. *Biochem. Biophys. Rs. Commun.* 88, 1223–1229; Hong, C. I., Nechaev, A., Kirisits, A. J. Buchheit, D. J. and West, C. R. (1980) Nucleoside conjugates as potential antitumor agents. 3. 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Combination or Alternation Therapy

It has been recognized that drug-resistant variants of HBV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in the viral life cycle, and most typically in the case of HBV, DNA polymerase. Recently, it has been demonstrated that the efficacy of a drug against HBV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

The anti-hepatitis B viral activity of β-L-2'-dA, β-L-2'-dC, β-L-2'-dU, β-L-2'-dG, β-L-2'-dT, β-L-dI, or other β-L-2'-nucleosides provided herein, or the prodrugs, phosphates, or salts of these compounds, can be enhanced by administering two or more of these nucleosides in combination or alternation. Alternatively, for example, one or more of β-L-2'-dA, β-L-2'-dC, β-L-2'-dU, β-L-2'-dG, β-L-2'-dT, β-L-dI, or other β-L-2'-nucleosides provided herein can be administered in combination or alternation with 3TC, FTC, L-FMAU, DAPD, famciclovir, penciclovir, BMS-200475, bis pom PMEA (adefovir, dipivoxil); lobucavir, ganciclovir, or ribavarin.

In any of the embodiments described herein, if the β-L-2'-nucleoside of the present invention is administered in combination or alternation with a second nucleoside or nonnucleoside reverse transcriptase inhibitor that is phosphorylated to an active form, it is preferred that a second compound be phosphorylated by an enzyme that is different from that which phosphorylates the selected β-L-2'-nucleoside of the present invention in vivo. Examples of kinase enzymes are thymidine kinase, cytosine kinase, guanosine kinase, adenosine kinase, deoxycytidine kinase, 5'-nucleotidase, and deoxyguanosine kinase.

Preparation of the Active Compounds

The 2'-deoxy-β-L-erythro-pentofuranonucleoside derivatives of the present invention are known in the art and can

be prepared according to the method disclosed by Holy, *Collect. Czech. Chem. Commun.* (1972), 37(12), 4072–87 and *Mol. Phys.* (1967), 3(4), 386–95.

A general process for obtaining β-L-erythro-pentafuranonucleosides (β-L-dN) is shown in FIG. 1, using L-ribose or L-xylose as a starting material.

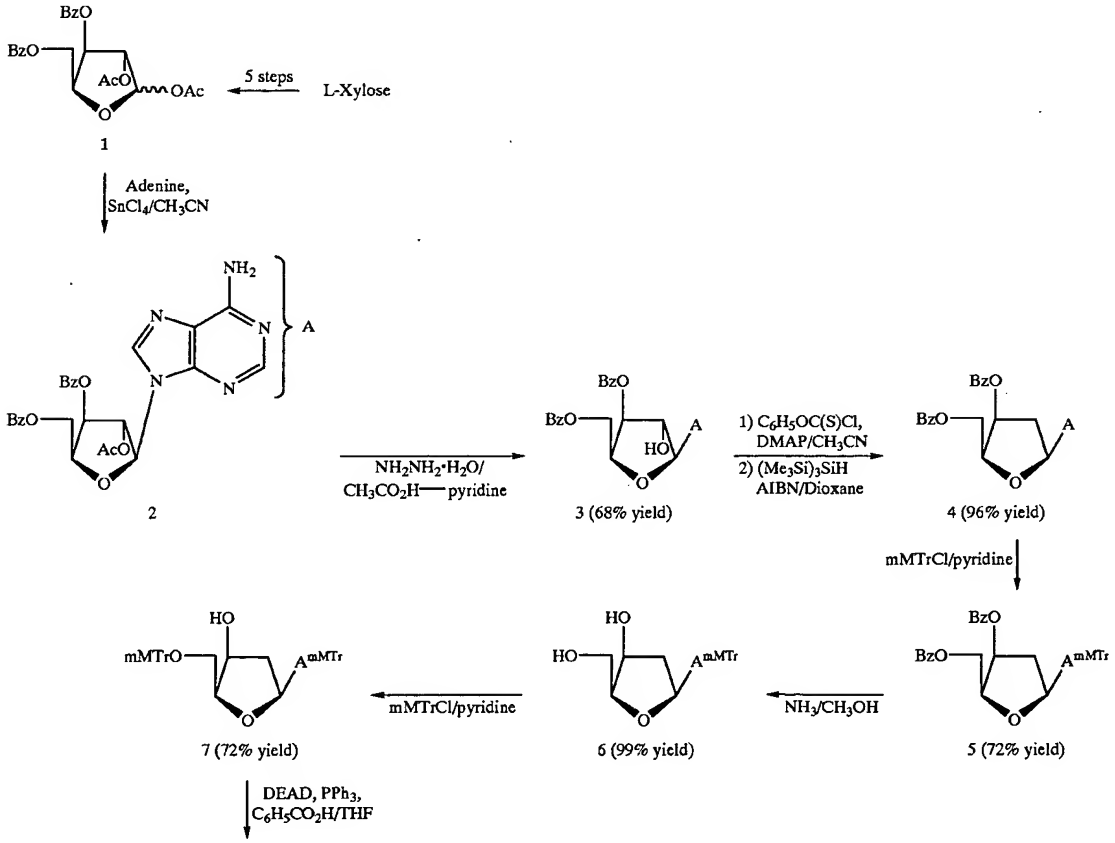
Mono, di, and triphosphate derivatives of the active nucleosides can be prepared as described according to published methods. The monophosphate can be prepared according to the procedure of Imai et al., *J. Org. Chem.*, 34(6), 1547–1550 (June 1969). The diphosphate can be prepared according to the procedure of Davisson et al., *J. Org. Chem.*, 52(9), 1794–1801 (1987). The triphosphate can be prepared according to the procedure of Hoard et al., *J. Am. Chem. Soc.*, 87(8), 1785–1788 (1965).

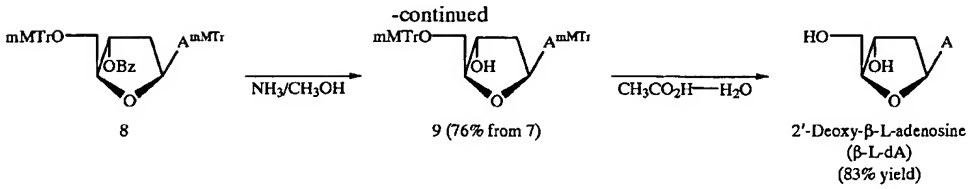
Experimental Protocols

Melting points were determined in open capillary tubes on a Gallenkamp MFB-595–010 M apparatus and are uncorrected. The UV absorption spectra were recorded on an Uvikon 931 (KONTRON) spectrophotometer in ethanol. ^{1}H-NMR spectra were run at room temperature in DMSO-d_6 with a Bruker AC 250 or 400 spectrometer. Chemical shifts are given in ppm, DMSO-yd_5 being set at 2.49 ppm as reference. Deuterium exchange, decoupling experiments or 2D-COSY were performed in order to confirm proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), m (multiplet). All J-values are in Hz. FAB mass spectra were recorded in the positive-(FAB>0) or negative-(FAB<0) ion mode on a JEOL DX 300 mass spectrometer The matrix was 3-nitrobenzyl alcohol (NBA) or a mixture (50:50, v/v) of glycerol and thioglycerol (GT). Specific rotations were measured on a Perkin-Elmer 241 spectropolarimeter (path length 1 cm) and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analysis were carried out by the "Service de Microanalyses du CNRS, Division de Vemaison" (France). Analyses indicated by the symbols of the elements or fuinctions were within ±0.4% of theoretical values. Thin layer chromatography was performed on pre-coated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualisation of products being accomplished by UV absorbency followed by charring with 10% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385) at atmospheric pressure.

EXAMPLE 1

Stereospecific Synthesis of 2'-Deoxy-β-L-Adenosine





9-(3,5-di-O-Benzoyl-β-L-xylofuranosyl)adenine (3)

A solution of 9-(2-O-acetyl-3,5-di-O-benzoyl-β-L-xylofuranosyl)adenine 2 [Ref: Gosselin, G.; Bergogne, M.-C.; Imbach, J.-L., "Synthesis and Antiviral Evaluation of β-L-Xylofuranosyl Nucleosides of the Five Naturally Occuring Nucleic Acid Bases", *Journal of Heterocyclic Chemistry*, 1993, 30 (Oct.-Nov.), 1229–1233] (8.30 g, 16.05 mmol) and hydrazine hydrate 98% (234 mL, 48.5 nunol) in a mixture of pyridine/glacial acetic acid (4/1, v/v, 170 mL) was stirred at room temperature for 22 h. The reaction was quenched by adding acetone (40 mL) and stirring was continued for one additional hour. The reaction mixture was reduced to one half of its volume, diluted with water (250 mL) and extracted with chloroform (2×150 mL). The organic layer was washed successively with an aqueous saturated solution of $NaHCO_3$ (3×100 mL) and water (3×100 mL), dried, filtered, concentrated and co-evaporated with toluene and methanol. The residue was purified by silica gel column chromatography (0–3% MeOH in dichloromethane) to give 3 (5.2 g, 68%) precipitated from diisopropylic ether: ^1H NMR (DMSO-d_6): δ 4.5–4.9 (m, 4H, H-2', H-4', H-5' and H-5"), 5.64 (t, 1H, H-3', $J_{2',3'}=J_{3',4'}=3.5$ Hz), 6.3 (br s, 1H, OH-2'), 6.45 (d, 1H, H-1', $J_{1',2'}=4.6$ Hz), 7.3 (br s, 2H, $NH_{2\text{-}6}$), 7.4–7.9 (m, 10H, 2 benzoyls), 8.07 and 8.34 (2s, 2H, H-2 and H-8); ms matrix G/T, (FAB^+) m/z 476 $[M+H]^+$, 136 $[BH_2]^+$, (FAB^-) m/z 474 $[M-H]^-$, 134 $[B]^-$; UV (95% ethanol): λ_{max} 257 nm (ε16400), 230 nm (ε 29300), λ_{min} 246 nm (ε 14800); $[\alpha]_D^{20}=-64$ (c 1.07, $CHCl_3$). Anal. Calcd for $C_{24}H_{21}N_5O_4$ (M=475.45): C, 60.43; H, 4.45; N, 14.73. Found: C, 60.41; H, 4.68; N, 14.27.

9-(3,5-di-O-Benzoyl-2-deoxy-β-L-threo-pentofuranosyl) adenine (4).

To a solution of compound 3 (1.00 g, 2.11 mmol) in dry acetonitrile (65 mL) were added 4-(dimethylamino)pyridine (0.77 g, 6.32 mmol) and phenoxythiocarbonyl chloride (0.44 mL, 3.16 mmol). The mixture was stirred at room temperature for 2 h. After concentration, the residue was dissolved in dichloromethane (50 mL) and washed successively with water (2×30 mL), aqueous solution of hydrochloric acid 0.5 N (30 mL) and water (3×30 mL). The organic layer was dried, filtered and concentrated to dryness. The crude thiocarbonylated intermediate was directly treated with tris-(trimethylsilyl)silane hydride (0.78 mL, 5.23 mmol) and α,α'-azoisobutyronitrile (AIBN, 0.112 g, 0.69 mmol) in dry dioxane (17 mL) at reflux for 2 h. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (0–5% MeOH in dichloromethane) to give pure 4 (0.93 g, 96%) as a foam: ^1H NMR (DMSO-d_6): δ 2.9–3.1 (m, 2H, H-2' and H-2"), 4.6–4.7 (m, 3H, H-4', H-5' and H-5"), 5.8 (br s, 1H, H-3'), 6.43 (dd, 1H, H-1', $J_{1',2'}=3.1$ Hz, $J_{1',2''}=7.6$ Hz), 7.3 (br s, 2H, $NH_{2\text{-}6}$), 7.4–7.9 (m, 10H, 2 benzoyls), 8.05 and 8.33 (2s, 2H, H-2 and H-8); ms : matrix G/T, (FAB^+) m/z 460 $[M+H]^+$, 325 $[S]^+$, 136 $[BH_2]^+$, (FAB^-) m/z 458 $[M-H]^-$, 134 $[B]^-$; UV (95% ethanol): λ_{max} 261 mn (ε 14400), 231 nm (ε 26300), λ_{min} 249 nm (ε 12000); $[\alpha]_D^{20}=-38$ (c 1.04, DMSO).

6-N-(4-Monomethoxytrityl)-9-(3,5-di-O-benzoyl-2-deoxy-β-L-threo-pentofuranosyl)adenine (5).

To a solution of compound 4 (0.88 g, 1.92 mmol) in dry pyridine (40 mL) was added 4-monomethoxytrityl chloride (1.18 g, 3.84 mmol). The mixture was stirred at 60° C. for 24 h. After addition of methanol (5 mL), the solution was concentrated to dryness, the residue was dissolved in dichloromethane (50 mL) and washed successively with water (30 mL), aqueous saturated $NaHCO_3$ (30 mL) and water (30 mL). The organic layer was dried, filtered, concentrated and co-evaporated with toluene to give pure 5 (1.01 g, 72%) as a foam: ^1H NMR ($CDCl_3$): δ 2.9–3.0 (m, 2H, H-2' and H-2"), 3.62 (s, 3H, OCH_3), 4.6–4.8 (m, 3H, H-4', H-5' and H-5"), 5.85 (pt, 1H, H-3"), 6.44 (dd, 1H, H-1', $J_{1',2'}=3.1$ Hz, $J_{1',2''}=7.3$ Hz), 6.9 (br s, 1H, NH-6), 6.7–6.8 and 7.2–7.4 (2m, 24H, 2 benzoyls and MMTr), 7.97 and 8.13 (2s, 2H, H-2 and H-8); ms: matri G/T, (FAB^+) m/z 732 $[M+H]^+$, (FAB^-) m/z 730 $[M-H]^-$[31] ; UV (95% ethanol): λ_{max} 274 nm (ε 12100), 225 nm (ε 24200), λ_{min} 250 nm (ε 5900); $[\alpha]_D^{20}=-16$ (c 1.12, DMSO).

6-N-(4-Monomethoxytrityl)-9-(2-deoxy-β-L-threo-pentofuranosyl)-adenine (6).

Compound 5 (0.95 g, 1.30 mmol) was treated with a solution (saturated at −10° C.) of methanolic ammonia (40 mL), at room temperature overnight. After concentration, the residue was dissolved in dichloromethane (60 mL) and washed with water (30 mL). The aqueous layer was extracted twice with dichloromethane (10 mL). The combined organic layer was dried, filtered and concentrated. The residue was purified by silica gel column chromatography (0–5% MeOH in dichloromethane) to give pure 6 (0.67 g, 98%) as a foam: ^1H NMR ($CDCl_3$): δ 2.6–2.9 (m, 2H, H-2' and H-2"), 3.5 (br s, 1H, OH-5'), 3.55 (s, 3H, OCH_3), 3.9–4.0 (m, 3H, H-4', H-5' and H-5"), 4.5–4.6 (m, 1H, H-3'), 6.03 (dd, 1H, H-1', $J_{1',2'}=4.0$ Hz, $J_{1',2''}=8.8$ Hz), 7.0)br s, 1H, NH-6), 6.7–6.8 and 7.1–7.4 (2m, 14H, MMTr), 7.40 (d, 1H, OH-3', $J_{H,OH}$ =10.6 Hz), 7.80 and 7.99 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB^+) m/z 524 $[M+H]^+$, 408 $[BH_2]^+$, (FAB^-) m/z 1045 $[2M-H]^-$, 522 $[M-H]^-$, 406 $[B]^-$; UV (95% ethanol): λ_{max} 275 nm (ε 12300), λ_{min} 247 nm (ε 3600); $[\alpha]_D^{20}=+28$ (c 0.94, DMSO).

6-N-(4-Monomethoxytrityl)-9-(2-deoxy-5-O-(4-monomethoxytrityl)-β-L-threo-pentofuranosyl)adenine (7).

Compound 6 (0.62 g, 1.24 mmol) in dry pyridine (25 mL) was treated with 4-monomethoxytrityl chloride (0.46 g, 1.49 mmol) at room temperature for 16 h. After addition of methanol (5 mL), the mixture was concentrated to dryness. The residue was dissolved in dichloromethane (60 mL) and washed successively with water (40 mL), a saturated aqueous solution of $NaHCO_3$ (40 mL) and water (3×40 mL). The organic layer was dried, filtered, concentrated and co-evaporated with toluene and methanol. The residue was purified by silica gel column chromatography (0–10% MeOH in dichloromethane) to give 7 (0.71 g, 72%) as a foam: ^1H NMR (DMSO-d_6): δ 2.21 (d, 1H, H-2'$J_{2',2''}$=14.3 Hz), 2.6–2.7 (m, 1H, H-2"), 3.1–3.3 (2m, 2H, H-5' and H-5"), 3.64 and 3.65 (2s, 6H, 2×OCH_3), 4.1–4.2 (m, 1H, H-4'), 4.2–4.3 (m, 1H, H-3'), 5.68 (d, 1H, OH-3', $J_{H,OH}$=5.2

Hz), 6.24 (d, 1H, H-1', $J_{1',2'}$=7.0 Hz), 6,7–6.8 and 7.1–7.3 (2m, 29H, 2 MMTr and NH-6), 7.83 and 821 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB$^+$) m/z 796 $[M+H]^+$, 408 $[BH_2]^+$, (FAB$^-$) m/z 794 $[M-H]^-$, 406 [B]_; UV (95% ethanol): λ_{max} 275 nm (ϵ 30900), λ_{min} 246 nm (ϵ 12800); $[\alpha]_D^{20}$=+14 (c 1.03, DMSO).

6-N-(4-Monomethoxytrityl)-9-(3-O-benzoyl-2-deoxy-5-(4-mono-metboxytrityl)-β-L-erythro-pentofuranosyl)adenine (8).

A solution of diethylazodicarboxylate (0.38 mL, 2.49 mmol) in dry tetrahydrofuran (20 mL) was added dropwise to a cooled solution (0° C.) of nucleoside 7 (0.66 g, 0.83 mmol), triphenylphosphine (0.66 g, 2.49 mmol) and benzoic acid (0.30 g, 2.49 mmol) in dry THF (20 mL). The mixture was stirred at room temperature for 18 h and methanol (1 mL) was added. The solvents were removed under reduced pressure and the crude material was purified by silica gel column chromatography (0–5% ethyl acetate in dichloromethane) to give compound 8 slightly contaminated by triphenylphosphine oxide.

6-N-(4-Monomethoxytrityl)-9-(2-deoxy-5-O-(4-monomethoxytrityl)-β-L-erythro-pentofuranosyl)adenine (9).

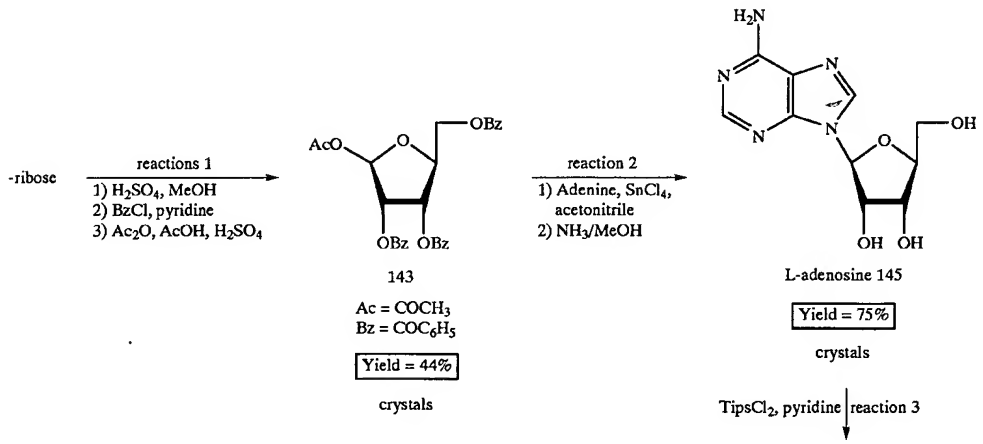
Compound 8 was treated by a solution (saturated at –10° C.) of methanolic ammonia (20 mL), at room temperature for 24 h, then the reaction mixture was concentrated to dryness. The residue was dissolved in dichloromethane (30 mL) and washed with water (20 mL). The aqueous layer was extracted by dichloromethane (2×20 mL) and the combined organic phase was dried, filtered and concentrated. Pure compound 9 (0.50 g, 76% from 7) was obtained as a foam after purification by silica gel column chromatography (0–2% MeOH in dichloromethane): ^{1}H NMR (DMSO-d_6): δ 2.2–2.3 (m, 1H, H-2'), 2.8–2.9 (m, 1H, H-2"), 3.1–3.2 (m, 2H, H-5' and H-5"), 3.64 and 3.65 (2s, 6H, 2×OCH_3), 3.97 (pq, 1H, H-4'), 4.4–4.5 (m, 1H, H-3'), 5.36 (d, 1H, OH-3', $J_{H,OH}$=4.5 Hz), 6.34 (t, 1H, H-1', $J_{1',2'}$=$J_{1',2'}$=6.4 Hz), 6.8–6.9 and 7.1–7.4 (2m, 29H, 2 MMTr and NH-6), 7.81 and 8.32 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB$^+$) m/z 796 $[M+H]^+$, 408 $[BH_2]^+$, (FAB$^-$) m/z 794 $[M-H]^-$, 406 $[B]^-$; UV (95% ethanol): λ_{max} 276 nm (ϵ 42600), λ_{min} 248 nm (ϵ 23300); $[\alpha]_D^{20}$=+29 (c 1.05, DMSO).

2'-Deoxy-β-L-adenosine (β-L-dA)

Compound 9 (0.44 g, 0.56 mmol) was treated with an aqueous solution of acetic acid 80% (17 mL) at room temperature for 5 h. The mixture was concentrated to dryness, the residue was dissolved in water (20 mL) and washed with diethyl ether (2×15 mL). The aqueous layer was concentrated and co-evaporated with toluene and methanol. The desired 2'-deoxy-β-L-adenosine (β-L-dA) (0.12 g, 83%) was obtained after purification by silica gel column chromatography (0–12% MeOH in dichloromethane) and filtration through a Millex HVA unit (0.45μg, Millipore): mp 193–194° C. (crystallized from water)(Lit. 184–185° C. for L-enantiomer [Ref.: Robins, M. J.; Khwaja, T. A.; Robins, R. K. *J. Org. Chem.* 1970, 35, 636–639] and 187–189° C. for D-enantiomer [Ref.: Ness, R. K. in *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; J. Wiley and sons: New York, 1968; Vol 1, pp 183–187]; ^{1}H NMR (DMSO-d_6): δ 2.2–2.3 and 2.6–2.7 (2m, 2H, H-2' and H-2"), 3.4–3.6 (2m, 2H, H-5' and H-5") 3.86 (pq, 1H, H4'), 4.3–4.4 (m, 1H, H-3'), 5.24 (t, 1H, OH-5', $J_{H,OH}$=5.8 Hz), 5.30 (d,1H, OH-3', $J_{H,OH}$=4.0 Hz), 6.32 (dd, 1H, H-1', $J_{1',2'}$=6.2 Hz, $J_{1',2'}$=7.8 Hz), 7.3 (br s, 2H, NH_{2-6}), 8.11 and 8.32 (2s, 2H, H-2 and H-8); ms: matrix G/T, (FAB$^+$) m/z 252 $[M+H]^+$, 136 $[BH_2]^+$, (FAB$^-$) m/z 250 $[M-H]^-$, 134 $[B]^-$; UV (95% ethanol): λ_{max} 258 nm (ϵ 14300), λ_{min} 226 nm (ϵ 2100); $[\alpha]_D^{20}$=+25 (c 1.03, H_2O), (Lit. $[\alpha]_D^{20}$=+23 (c 1.0, H_2O) for L-e3nantiomer [Ref.: Robins, M. J.; Khwaja, T. A.; Robins, R. K. *J. Org. Chem.* 1970, 35, 636–639] and $[\alpha]_D^{20}$=–25 (c 0.47, H_20) for D-enantiomer [Ref.: Ness, R. K. in *Synthetic Procedures in Nucleic Acid Chemistry*, Zorbach, W. W., Tipson, R. S., Eds.; J. Wiley and sons: New York, 1968; Vol 1, pp 183–187]). Anal. Calcd for $C_{10}H_{13}N_5O_3$+1.5 H_2O (M=278.28): C, 43.16; H, 5.80; N, 25.17. Found: C, 43.63; H, 5.45; N, 25.33.

EXAMPLE 2

Stereoselective Synthesis of 2'-Deoxy-β-L-Adenosine (β-L-dA)



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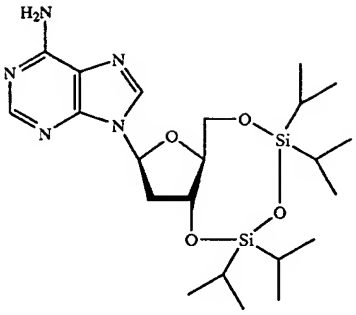
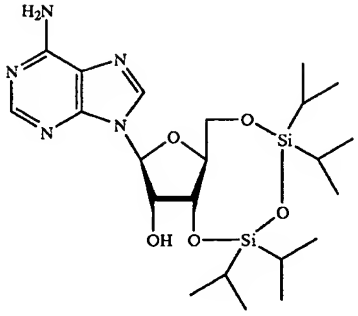


148
1 chromatography column

Yield = 70%

foam

reactions 4
1) PhOCSCl, DMAP, acetonitrile
2) TTMSS, AIBN, dioxane

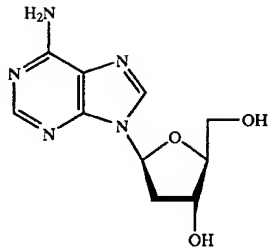


146

Yield = 90%

crystals

reaction 5 NH_4F, MeOH

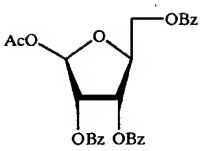


L-deoxyadenosine 149
1 chromatography column

Yield = 75%

crystals

-continued



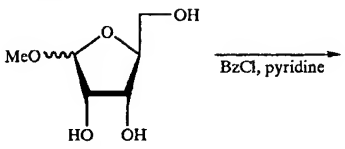
143

Yield = 44%

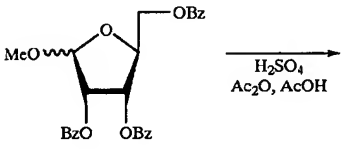
crystals

Reaction 1:

L-ribose $\xrightarrow{H_2SO_4, MeOH}$



141



142

Precursor: L-ribose (Cultor Science Food, CAS [24259-59-4], batch RIB9711013)

Reactants: Sulphuric acid 95–97% (Merck; ref 1.00731.1000); Benzoyl chloride (Fluka; ref 12930); Sodium sulfate (Prolabo; ref 28111.365)

Solvents: Methanol P.A. (Prolabo; ref 20847.295); Pyridine 99% (Acros; ref 131780025); Dichloromethane P.A. (Merck; ref 1.06050.6025); Acetic acid P.A. (carlo erba; ref 20104298); Acetic anhydride (Fluka; ref 45830); Ethanol 95 (Prolabo; ref 20823.293)

References: Recondo, E. F., and Rinderknecht, H., Eine neue, Einfache Synthese des 1-O-Acetyl-2,3,5-Tri-O-β-D-Ribofuranosides. *Helv. Chim. Acta*, 1171–1173 (1959).

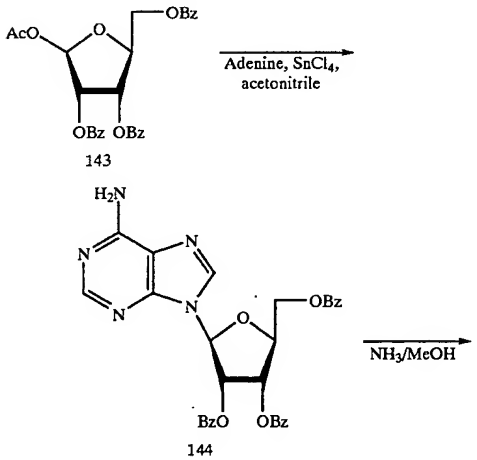
A solution of L-ribose 140 (150 g, 1 mol) in methanol (2 liters) was treated with sulphuric acid (12 ml) and left at +4°

C. for 12 hrs, and then neutralised with pyridine (180 ml). Evaporation gave an α,β mixture of methyl ribofuranosides 141 as a syrup. A solution of this anomeric mixture in pyridine (1.3 liters) was treated with benzoyl chloride (580 ml, 5 mol) with cooling and mechanical stirring. The solution was left at room temperature for 12 hrs and then poured on ice (about 10 liters) with continued stirring. The mixture (an oil in water) was filtered on a Cellite bed. The resulting oil on the cellite bed was washed with water (3×3 liters) and then dissolved with ethyl acetate (3 liters). The organic phase was washed with a 5% $NaHCO_3$ solution (2 liters) and water (2 liters), dried over sodium sulfate, filtered and evaporated to give 1-O-methyl-2,3,5-tri-O-benzoyl-a/β-L-ribofuranose 142 as a thick syrup. The oil was dissolved in acetic anhydride (560 ml) and acetic acid (240 ml). The solution was, after the dropwise addition of concentrated sulphuric acid (80 ml), kept in the cold (+4° C.) under mechanical stirring for 10 hrs. The solution was then poured on ice (about 10 liters) under continued stirring. The mixture (oily compound in water) was filtered on a Cellite bed. The resulting gummy solid on the cellite bed was washed with water (3×3 liters) and then dissolved in dichloromethane (2,5 liters). The organic phase was washed with 5% $NaHCO_3$ (1 liter) and water (2×2 liters), dried over sodium sulfate, filtered and evaporated to give a gummy solid 143, which was crystallized from ethanol 95 (yield 225 g, 44%).

Analyses for 1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose 143:

mp 129–130° C. (EtOH 95) (lit.(1) mp 130–131° C.) ^1H NMR (200 MHz, $CDCl_3$): δ 8.09–7.87 (m, 6H, H_{Arom}), 7.62–7.31 (m, 9H, H_{Arom}) 6.43 (s, 1H, H1), 5.91 (dd, 1H, H_3, $J_{3,4}$ 6.7 Hz; $J_{3,2}$ 4.9 Hz), 5.79 (pd, 1H, H_2, $J_{2,3}$ 4,9 Hz; $J_{1,2}$ <1), (s,2H, H4 and H_5), 4,51 (dd, 1H, H_5, $J_{5,5'}$13,1 Hz, $J_{5',4}$ 5,5 Hz), 2,00 (s, 3H, CH_3CO); (identical to commercial 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose); Mass analysis (FAB+, GT) m/z 445 (M-OAc)+; Elemental analysis $C_2H_{24}O_9$ Calculated C 66.66 H 4.79; found C H.

Reaction 2:



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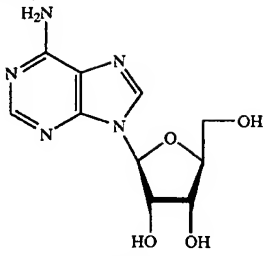


L-adenosine 145

Yield = 75%

crystals

Precursor: Adenine (Pharma-Waldhof; ref 400134.001 lot 45276800)

Reactants: Stannic chloride furming (Fluka; ref 96558); NH_3/Methanol (methanol saturated with NH_3; see page 5); Sodium sulfate (Prolabo; ref 28111.365)

Solvents: Acetonitrile (Riedel-de Hean; ref 33019; distilled over CaH_2); Chloroform Pur (Acros; ref 22706463); Ethyl acetate Pur (Carlo erba; ref 528299)

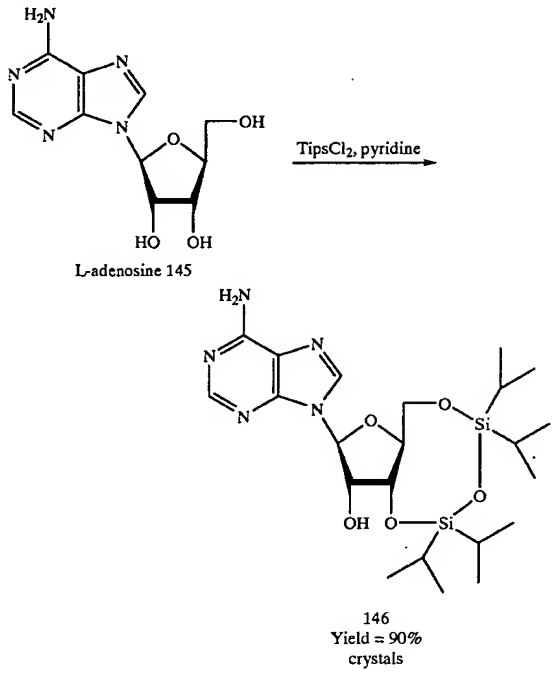
References: Saneyoshi, M., and Satoh, E., Synthetic Nucleosides and Nucleotides. XIII. Stannic Chloride Catalyzed Ribosylation of Several 6-Substituted Purines. *Chem; Pharm. Bull.*, 27, 2518–2521 (1979).; Nakayarna, C., and Saneyoshi, M., Synthetic Nucleosides and Nucleotides. XX. Synthesis of Various 1-β-Xylofuranosyl-5-Alkyluracils and Related *Nucleosides. Nucleosides, Nucleotides*, 1, 139–146 (1982).

Adenine (19.6 g, 144 mmol) was suspended in acetonitrile (400 ml) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose 143 (60 g, 119 mmol). To this suspension was added stannic chloride filming (22 ml, 187 mmol). After 12 hrs, the reaction was concentrated to a small volume (about 100 ml), and sodium hydrogencarbonate (110 g) and water (120 ml) were added. The resulting white solid (tin salts) was extracted with hot chloroform (5×200 ml). The combined extracts were filtered on a cellite bed. The organic phase was washed with a $NaHCO_3$ 5% solution and water, dried over sodium sulfate, filtered and evaporated to give compound 144 (60 g, colorless foam). The foam was treated with methanol saturated with ammonia (220 ml) in sealed vessel at room temperature under stirring for 4 days. The solvent was evaporated off under reduced pressure and the resulting powder was suspended in ethyl acetate (400 ml) at reflux for 1 hr. After filtration, the powder was recrystallized from water (220 ml) to give L-adenosine 145 (24 g, crystals, 75%)

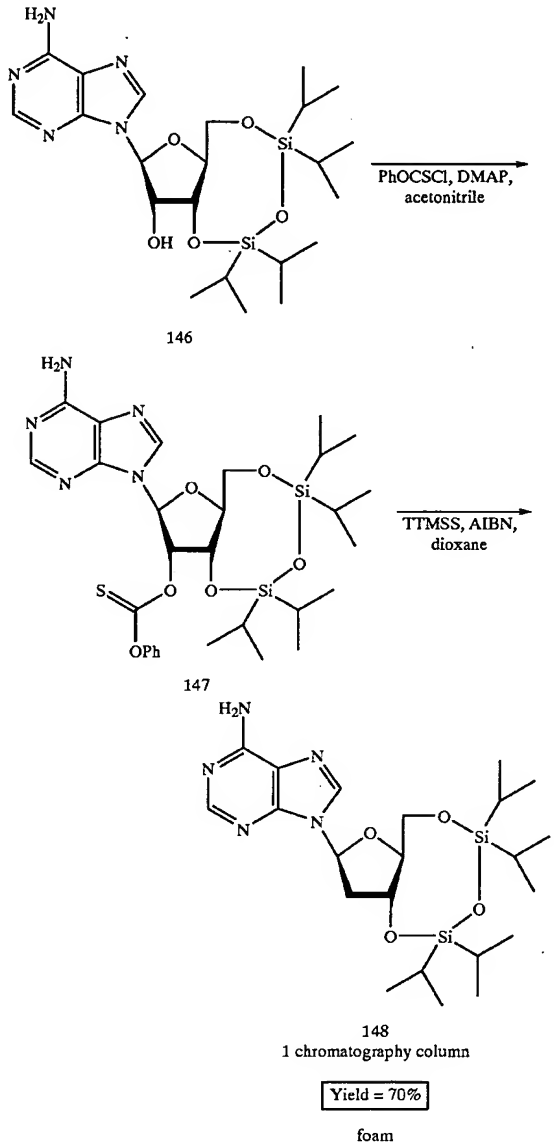
Analyses for β-Ladenosine:

mp 233–234° C. (water) (lit.(4) mp 235°–238° C.) ^1H NMR (200 MHz, DMSO-D_6): δ 8.34 and 8.12 (2s, 2H, H_2 and H_8), 7.37 (1s, 2H, NH_2), 5.86 (d, 1H, $H_{1'}$, $J_{1',2'}$6.2 Hz), 5.43 (m, 2H, $OH_{2'}$and $OH_{5'}$), 5.19 (d, 1H, OH3', J 3.7 Hz), 4,60 (m, $H_{2'}$), 4.13 (m, 1H, $H_{3'}$), 3.94 (m, 1H, $H_{4'}$), 3.69–3.49 (m, 2H, $H_{5'a}$ and $H_{5'b}$), (identical to commercial D-adenosine); Mass analysis (FAB+, GT) m/z 268 $(M+H)^+$, 136$(BH_2)^+$.

Reaction 3:



Reaction 4:



Reactants: 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (Fluka; ref 36520); Sodium sulfate (Prolabo; ref 28111.365)

Solvents: Pyridine 99% (Acros; ref 131780025); Ethyl acetate Pur (Carlo erba; ref 528299); Acetonitrile (Riedel-de Haen; ref 33019)

Reference: Robins, M. J., et al., Nucleic Acid Related Compounds. 42. A General Procedure for the Efficient Deoxygenation of Secondary Alcohols. Regiospecific and Stereoselective Conversion of Ribonucleosides to 2'-Deoxynucleosides. *J. Am. Chem. Soc.* 105, 4059–4065 (1983).

To L-adenosine 145 (47,2 g, 177 mmol) suspended in pyridine (320 ml) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (63 ml, 201 mmol), and the mixture was stirred at room temperature for 12 hrs. Pyridine was evaporated and the residue was partitioned with ethyl acetate (1 liter) and a $NaHCO_3$ 5% solution (600 ml). The organic phase was washed with a HCl 0.5N solution (2×500 ml) and water (500 ml), dried over sodium sulfate, filtered and evaporated to dryness. The resulting solid was crystallized from acetonitrile to give compound 146 (81 g, 90%).

Analyses 3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-β-L-adenosine 146:

mp 97–98° C. (acetonitrile) (lit. (5) D enantiomer mp 98° C.) ^1H NMR (200 MHz, $CDCl_3$): δ 8.28 and 7.95 (2s, 2H, H_2 and H_8), 5.96 (d, 1H, $J_{1',2'}$1,1 Hz), 5.63 (s, 2H, NH_2), 5.10 (dd, 1H, $H_{3'}$, $J_{3',4'}$7.6 Hz, $J_{3',2'}$5.5 Hz), 4.57 (dd, 1H, $H_{2'}$, $J_{2',1'}$1.2 Hz; $J_{2',3'}$7.6 Hz), 4.15–3.99 (m, 3H, $H_{4'}$, $H_{5'a}$ and $H_{5'b}$), 3.31 (sl, 1H, $OH_{2'}$), 1.06 (m, 28H, isopropyl protons) Mass analysis (FAB-, GT) m/z 508 $(M-H)^-$, 134 $(B)^-$; (FAB+, GT) m/z 510 $(m+H)^+$, 136 $(BH_2)^+$;

Reactants: Dimethylaminopyridine 99% (Acros; ref 1482702050); Phenylchlorothionocarbonate 99% (Acros; ref 215490050), Tris(trimethylsilyl)silane "TTMSS" (Fluka; ref 93411); α,α'-Azoisobutyronitrile "AIBN" (Fluka, ref 11630); Sodium sulfate (Prolabo; ref 28111.365)

Solvents: Acetonitrile (Riedel-de Haen; ref 33019); Ethyl acetate Pur (Carlo Erba; ref 528299); Dioxan P. A. (Merck; ref 1.09671.1000); Dichloromethane (Merck; ref 1.06050.6025); Methanol (Carlo Erba; ref 309002);

Reference: Robins, M. J., Wilson, J. S., and Hansske, F., Nucleic Acid Related Compounds. 42. A General Procedure for the Efficient Deoxygenation of Secondary Alcohols. Regiospecific and Stereoselective Conversion of Ribonucleosides to 2'-Deoxynucleosides. *J. Am. Chem. Soc.*, 105, 4059–4065 (1983).

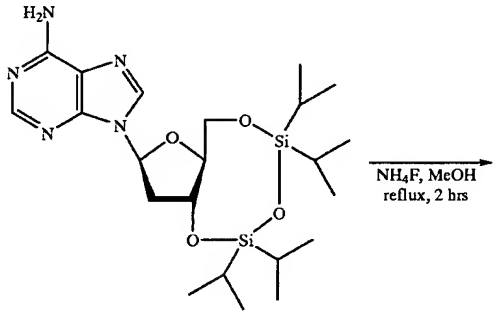
To compound 146 (34 g, 67 mmol) were added acetonitrile (280 ml), DMAP (16.5 g, 135 mmol) and phenyl

chlorothionocarbonate (10.2 ml, 73 mmol). The solution was stirred at room temperature for 12 hrs. Solvent was evaporated and the residue was partioned between ethyl acetate (400 ml) and a HCl 0.5N solution (400 ml). The organic layer was washed with a HCl 0.5N solution (400 ml) and water (2×400 ml), dried over sodium sulfate, filtered and evaporated to dryness to give the intermediate as a pale yellow solid. The crude 147 was dissolved in dioxan (ml) and AIBN (3.3 g, 20 mmol) and TTMSS (33 ml, 107 mmol) were added. The solution was progressively heated until reflux and stirred for 2 hrs. The reaction was concentrated to a yellow oil which was chromatographed (eluent dichloromethane/methanol 95/5) to give compound 148 (23 g, colorless foam, 70%). An aliquot was cristallized from ethanol/petroleum ether.

Analyses for 3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2'-deoxy-β-L-adenosine 148:

mp 110–111° C. (EtOH/petroleum ether) (Lit.(5) mp 113–114° C. (EtOH)) ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.33 and 8.03 (2s, 2H, H_2 and H_8), 6.30 (dd, 1H, $H_{1'}$, J 2.85 Hz, J 7.06 Hz), 5.63 (s1, 2H, NH_2), 4.96 (m, 1H, $H_{3'}$), 4.50 (m, 2H, $H_{5'a}$ and $H_{5'b}$), 2,68 (m, 2H, $H_{2'a}$ and $H_{2'b}$), 1.08 (m, 28H, isopropyl protons) Mass analysis (FAB+, GT) m/z 494 $(M+H)^+$, 136 $(BH_2)^+$

Reaction 5:



148

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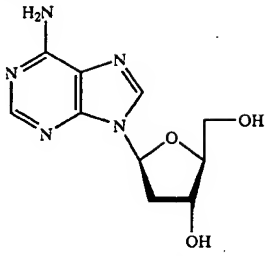


L-deoxyadenosine 149
1 chromatography column

Yield = 75%

crystals

Reactants: Ammonium fluoride (Fluka; ref 09742); Silica gel (Merck; ref 1.07734.2500)

Solvents: Methanol P.A. (Prolabo; ref 20847.295); Dichloromethane P.A. (Merck; ref 1.06050.6025); Ethanol 95 (Prolabo; ref 20823.293)

Reference: Zhang, W., and Robins, M. J., Removal of Silyl Protecting Groups from Hydroxyl Functions with Ammoniun Fluoride in Methanol. *Tetrahedron Lett.*, 33, 1177–1180 (192).

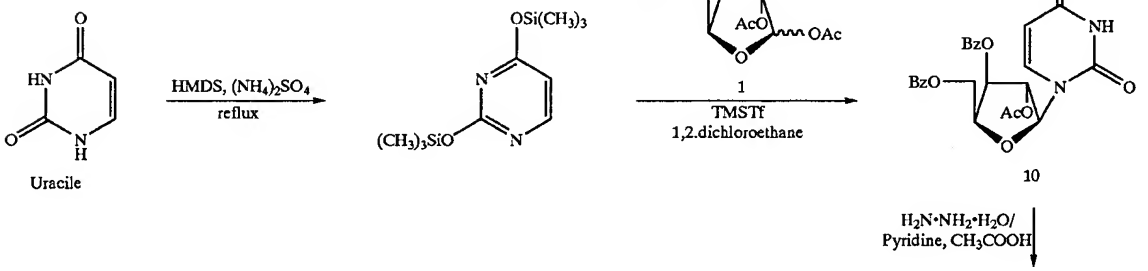
A solution of 3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2'-deoxy-L-adenosine 148 (32 g, 65 mmol) and ammonium fluoride (32 g, mmol) in methanol was stirred at reflux for 2 hrs. Silica gel was added and the mixture was carefully evaporated to give a white powder. This powder was added on the tpo of a silica column, which was eluted with dichloromethane/methanol 9/1. The appropriate fractions were combined and evaporated to give a white powder, which was crystallized from ethanol 95 (12.1 g, 75%).

Analyses for 2'-Deoxy-β-L-adenosine 149:

mp 189–190° C. (EtOH 95) (identical to commercial 2'-deoxy-D-adenosine) ^{1}H NMR (200 MHz, DMSO-D_6): δ 8.35 and 8.14 (2s, 2H, H_2 and H_8), 7.34 (s1, 2H, NH_2), 6.35 (dd, 1H, $H_{1'}$, J 6.1 Hz, J 7.85 Hz), 5.33 (d, 1H, $OH_{2'}$, J 4.0 Hz), 5.28 (dd, 1H, $H_{3'}$, J 4.9 Hz), 4.42 (m, 1H, OH5'), 3.88 (m, 1H, $H_{4'}$), 3.63–3.52 (m, 2H, $H_{5'a}$ and $H_{5'b}$), 2,71 (m, 1H, $H_{2'a}$), 2.28 (m, 1H, H2'b). (identical to commercial 2'-deoxy-D-adenosine) α_D+26° (c 0.5 water) (commercial 2'-deoxy-D-adenosine-25° (c 0.5 water)). UV λmax 260 nm (ε 14100) (H_2O). Mass analysis (FAB+, GT) m/z 252 $(M+H)^+$, 136 $(BH_2)^+$

EXAMPLE 3

Stereospecific Synthesis of 2'-Deoxy-β-L-Cytidine

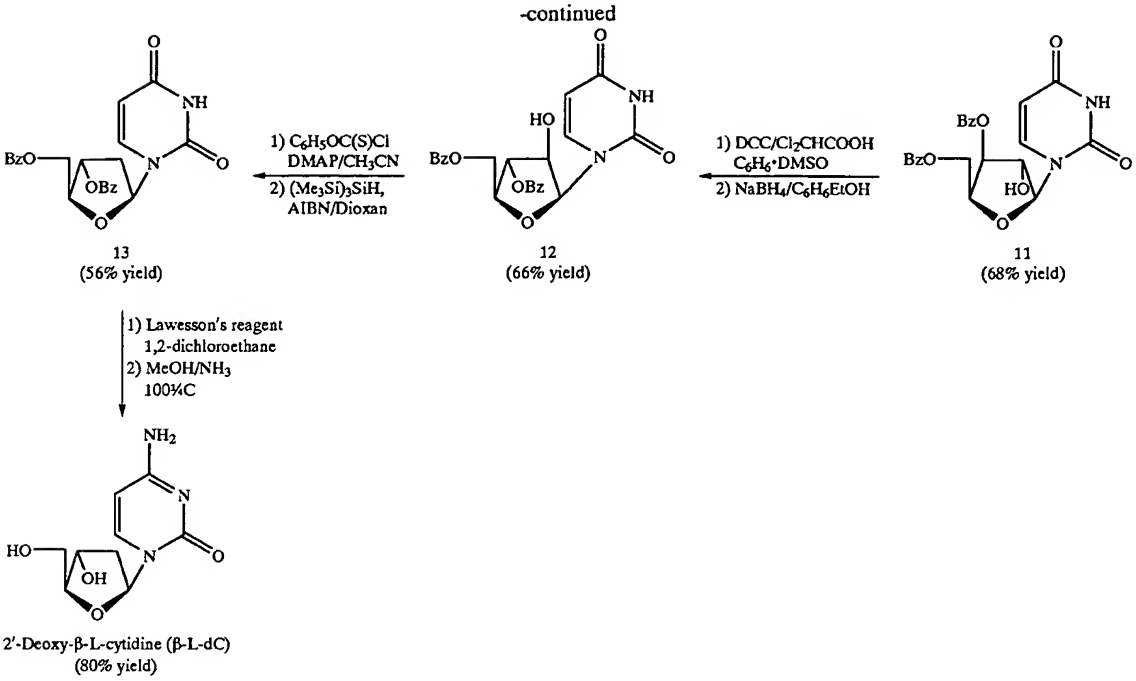


Uracile

1

10

-continued



1-(3,5-di-O-Benzoyl-β-L-xylofuranosyl)uracil (11)

Hydrazine hydrate (1.4 mL, 28.7 mmol) was added to a solution of 1-(2-O-acetyl-3,5-di-O-benzoyl-β-L-xylofuranosyl)uracil 10 [Ref.: Gosselin, G.; Bergogne, M.-C.; Imbach, J.-L., "Synthesis and Antiviral Evaluation of β-L-Xylofuranosyl Nucleosides of the Five Naturally Occuring Nucleic Acid Bases", Journal of Heterocyclic Chemistry, 1993, 30 (Oct.-Nov.), 1229–1233] (4.79 g, 9.68 mmol) in pyridine (60 mL) and acetic acid (15 mL). The solution was stirred overnight at room temperature. Acetone was added (35 mL) and the mixture was stirred for 30 min. The reaction mixture was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (0–4%) in dichloromethane to give 11 (3.0 g, 68%) which was crystallized from cyclohexane/dichloromethane: mp=111–114° C.; ^{1}H-NMR (DMSO-d_6): δ 11.35 (br s, 1H, NH), 7.9–7.4 (m, 11H, 2 C_6H_5CO, H-6), 6.38 (d, 1H, OH-2', $J_{OH\text{-}2'}$=4.2 Hz), 5.77 (d, 1H, H-1', $J_{1'\text{-}2'}$=1.9 Hz), 5.55 (d, 1H, H-5, $J_{5\text{-}6}$=8 Hz), 5.54 (dd, 1H, H-3', $J_{3'\text{-}2'}$=3.9 Hz and $J_{3'\text{-}4'}$=1.8 Hz), 4.8 (m, 1H, H-4'), 4.7 (m, 2H, H-5' and H-5"), 4.3 (m, 1H, H-2'); MS: FAB>0 (matrix GT) m/z 453 $(M+H)^+$, 105 $(C_6H_5CO)^+$; FAB<0 (matrix GT) m/z 451 $(M-H)^-$, 121 $(C_6H_5CO_2)^-$, 111 $(B)^-$; Anal. Calcd for $C_{23}H_{20}N_2O_8·H_2O$: C, 58.09; H, 4.76; N, 5.96. Found: C, 57.71; H, 4.42; N, 5.70.

1-(3,5-di-O-Benzoyl-β-L-arabinofuranosyl)uracil (12)

To a solution of 1-(3,5-di-O-benzoyl-β-L-xylofuranosyl) uracil 11 (8 g, 17.7 mL) in an anhydrous benzene-DMSO mixture (265 mL, 6:4, v/v) were added anhydrous pyridine (1.4 mL), dicyclohexylcarbodiimide (10.9 g, 53 mmol) and dichloroacetic acid (0.75 mL). The resulting mixture was stirred at room temperature for 4 h, then diluted with ethyl acetate (400 mL) and a solution of oxalic acid (4.8 g, 53 mmol) in methanol (14 mL) was added. After being stirred for 1 h, the solution was filtered. The filtrate was washed with a saturated NaCl solution (2×500 mL), 3% $NaHCO_3$ solution (2×500 mL) and water (2×500 mL). The organic phase was dried over Na_2SO_4, then evaporated under reduced pressure. The resulting residue was then solubilized in an EtOH absolute-benzene mixture (140 mL, 2:1, v/v). To this solution at 0° C. was added $NaBH_4$ (0.96 g, 26.5 mmol). After being stirred for 1 h, the solution was diluted with ethyl acetate (400 mL), then filtered. The filtrate was washed with a saturated NaCl, solution (400 mL) and water (400 mL). The organic phase was dried over Na_2SO_4, then evaporated under reduced pressure. The resulting crude material was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (0–3%) in dichloromethane to give 12 (5.3 g, 66%) which was crystallized from acetonitrile: mp=182–183° C.; ^{1}H-NMR (DMSO-d_6): δ 11.35 (br s, 1H, NH), 8.0–7.5 (m, 11H, 2 C_6H_5CO, H-6), 6.23 (br s, 1H, OH-2'), 6.15 (d, 1H, H-1', $J_{1'\text{-}2'}$=4 Hz), 5.54 (d, 1H, H-5, $J_{5\text{-}6}$ =8.1 Hz), 5.37 (t, 1H, H-3', $J_{3'\text{-}2'}$=$J_{3'\text{-}4'}$=2.6 Hz), 4.7–4.6 (m, 2H, H-5' and H-5"), 4.5 (m, 1H, H-4'), 4.4 (m, 1H, H-2'); MS: FAB>0 (matrix GT) m/z453 $(M+H)^+$, 341 $(S)^+$, 113 $(BH_2)^+$, 105 $(C_6H_5CO)^+$; FAB<0 (matrix GT) m/z 451 $(M-H)^-$, 121 $(C_6H_5CO_2)^-$, 111 $(B)^-$; Anal. Calcd for $C_{23}H_{20}N_2O_8$: C, 61.06; H, 4.46; N, 6.19. Found: C, 60.83; H, 4.34; N, 6.25.

1-(3,5-di-O-Benzoyl-2-deoxy-β-L-erythro-pentofuranosyl) uracil (13)

To a solution of 1-(3,5-di-O-benzoyl-β-L-arabinofuranosyl)uracil 12 (5.2 g, 11.4 mmoL) in anhydrous 1,2-dichloroethane (120 mL) were added phenoxythiocarbonyl chloride (4.7 mL, 34.3 mL) and 4-(dimethylamino) pyridine (DMAP, 12.5 g, 102.6 mmoL). The resulting solution was stirred at room temperature under argon atmosphere for 1 h and then evaporated under reduced pressure. The residue was dissolved in dichloromethane (300 mL) and the organic solution was successively washed with an ice-cold 0.2 N hydrochloric acid solution (3×200 mL) and water (2×200 mL), dried over Na_2SO_4 then evaporated under reduced pressure. The crude material was co-evaporated several times with anhydrous dioxane and dissolved in this solvent (110 mL). To the resulting solution

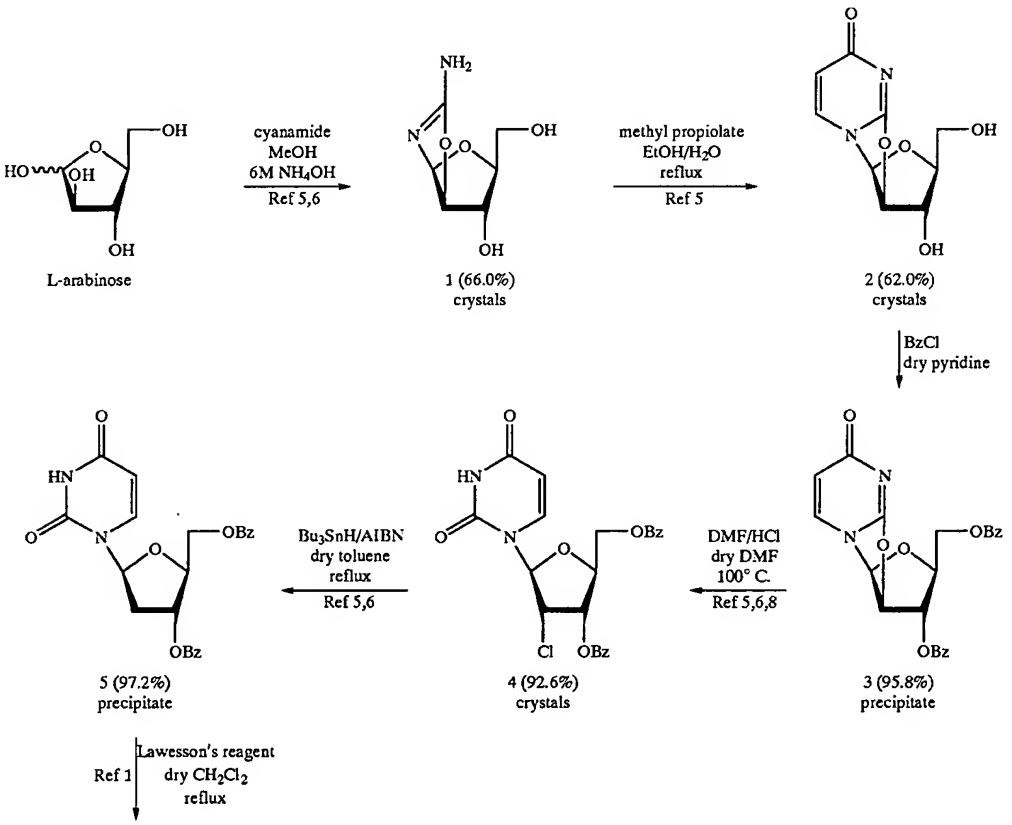
were added under argon tris-(trimethylsilyl)silane hydride (4.2 mL, 13.7 mmol) and α,α'-azoisobutyronitrile (AIBN, 0.6 g, 3.76 mmol). The reaction mixture was heated and stirred at 100° C. for 1 h under argon, then cooled to room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (0–5%)] to give 13 (2.78 g, 56%) which was crystallized from EtOH: mp=223–225° C.; H-NMR (DMSO-d_6): δ 11.4 (br s, 1H, NH), 8.0–7.5 (m, 11H, $2CH_6H_5CO$, H-6), 6.28 (t, 1H, H-1', J=7 Hz), 5.5 (m, 2H, H-1' and H-5), 4.6–4.4 (m, 3H, H-4', H-5' and H-5"), 2.6 (m, 2H, H-2' and H-2"); MS: FAB>0 (matrix GT) m/z 437 $(M+H)^+$, 3325 $(S)^+$; FAB<0 (matrix GT) m/z 435 $(M-H)^-$, 111 $(B)^-$; Anal. Calcd for $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: C, 62.98; H, 4.79; N, 6.40.

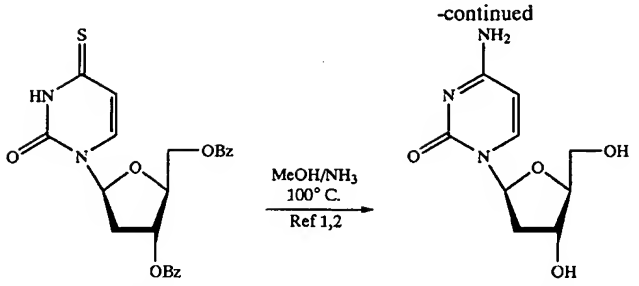
2'-Deoxy-β-L-cytidine (β-L-dC)

Lawesson's reagent (1.72 g, 4.26 mmol) was added under argon to a solution of 1-(3,5-di-O-benzoyl-2-deoxy-β-L-erythro-pentofuranosyl)uracil 13 (2.66 g, 6.1 mmol) in anhydrous 1,2-dichloroethane (12 mL) and the reaction mixture was stirred under reflux for 2 h. The solvent was then evaporated under reduced pressure and the residue was purified by silica gel column chromatography [eluent: stepwise gradient of ethyl acetate (0–8%) in dichloromethane] to give the 4-thio intermediate as a yellow foam. A solution of this thio-intermediate (1.5 g, 3.31 mmol) in methanolic ammonia (previously saturated at −10° C. and tightly stopped) (50 mL) was heated at 100° C. in a stainless-steel bomb for 3 h and then cooled to 0° C. The solution was evaporated under reduced pressure. The resulting crude material was purified by silica gel column chromatography [eluent: stepwise gradient of methanol(0–20%) in dichloromethane]. Finally, the appropriate fractions were pooled, filtered through a unit Millex HVA-4 (0,45 μm, Millipore) and evaporated under reduced pressure to provide the desired 2'-deoxy-β-L-cytidine (P-LdC) as a foam (0.6 g, 80%) which was crystallized from absolute EtOH: mp=198–199° C.; ^{1}H-NMR (DMSO-d_6): δ 7.77 (d, 1H, H-6, $J_{6\text{-}5}$=7.4 Hz), 7.10 (br d, 2H, NH_2), 6.13 (t, 1H, H-1', J=6.7 Hz), 5.69 (d, 1H, H-5, $J_{5\text{-}6}$=7.4 Hz), 5.19 (d, 1H, OH-3', $J_{OH\text{-}3'}$=4.1 Hz), 4.96 (t, 1H, OH-5', $J_{OH\text{-}5'}=J_{OH\text{-}5''}$=5.2 Hz), 4.1 (m, 1H, H-3'), 3.75 (m, 1H, H-4'), 3.5 (m, 2H, H-5' and H-5"), 2.0 (m, 1H, H-2'), 1.9 (m, 1H, H-2"); MS: FAB>0 (matrix GT) m/z 228 $(M+H)^+$, 112 $(BH_2)^+$; FAB<0 (matrix GT) m/z 226$(M-H)^-$; $[\alpha]^{20}_D$=−69 (c 0.52, DMSO) [[α] $^{20}_D$=+76 (c 0.55, DMSO) for a commercially available hydrochloride salt of the D-enantiomer]. Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.35; H, 5.68; N, 18.29.

EXAMPLE 4

Stereoselective Synthesis of 2'-Deoxy-β-L-Cytidine (β-L-dC)





6 (quantitatif) solid after purification

β-L-dC (78.6%) crystals

2-Amino-β-L-arabinofurano]1',2':4,5]oxazoline (1)

A mixture of L-arabinose (170 g, 1.13 mol), cyanamide (100 g, 2.38 mol), methanol (300 ml), and 6M-NH_4OH (50 ml) was stirred at room temperature for 3 days and then kept at −10° C. overnight. The product was collected with suction, washed successively with methanol and ether, and dried in vacuo. Yield, 130 g (66.0%) of the analytically pure compound 1, m.p. 170–172° C.; ^1H NMR (DMSO-d_6) δ ppm 6.35 (br s, 2H, NH_2), 5.15 (d, 1H, H-1, J=5.6 Hz), 5.45 (br s, 1H, OH-3), 4.70 (br s, 1H, OH-5), 4.55 (d, 1H, H-2, J=5.6 Hz), 4.00 (br s, 1H, H-3), 3.65 (m, 1H, H-4), 3.25 (m, 2H, H-5, H-5').

Reagents

L-arabinose: Fluka, >99.5%, ref 10839

Cyanamide: Fluka, >98%, ref 28330

$O^{2,2'}$-anhydro-β-L-uridine (2)

A solution of compound 1 (98.8 g, 0.57 mol) and methyl propiolate (98 ml) in 50% aqueous ethanol (740 ml) was refluxed for 5 h, then cooled and concentrated under diminished pressure to the half of the original volume. After precipitation with acetone (600 ml), the product was collected with suction, washed with ethanol and ether, and dried. The mother liquor was partialy concentrated, the concentrate precipitated with acetone (1000 ml), the solid collected with suction, and washed with acetone and ether to afford another crop of the product. Over-all yield, 80 g (62%) of compound 2, m.p. 236–240° C.; ^1H NMR (DMSO-d_6) δ ppm 7.87 (d, 1H, H-6, J=7.4 Hz), 6.35 (d, 1H, H-1', J=5.7 Hz), 5.95 (d, 1H, H-5, J=7.4 Hz), 5.90 (d, 1H, OH-3'), 5.20 (d, 1H, H-2', J=5.7 Hz), 5.00 (m, 1H, OH-3'), 4.44 (br s, 1H, H-3'), 4.05 (m, 1H, H-4'), 3.25 (m, 2H, H-5, H-5').

Reagent

Methyl propiolate: Fluka, >97%, ref 81863

3',5'-di-O-Benzoyl-$O^{2,2'}$-anhydro-β-L-uridine (3)

To a solution of compound 2 (71.1 g, 0.31 mol) in anhydrous pyridine (1200 ml) was added benzoyl chloride (80.4 ml) at 0° C. and under argon. The reaction mixture was stirred at room temperature for 5 h under exclusion of atmospheric moisture and stopped by addition of ethanol. The solvents were evaporated under reduced pressure and the resulting residue was coevaporated with toluene and absolute ethanol. The crude mixture was then diluted with ethanol and the precipitate collected with suction, washed successively with ethanol and ether, and dried. Yield, 129 g (95.8%) of compound 3, m.p. 254° C.; ^1H NMR (DMSO-d_6) δ ppm 8.1–7.4 (m, 11H, C_6H_5CO, H-6), 6.50 (d, 1H, H-1', J=5.7 Hz), 5.90 (d, 1H, H-5, J=7.5 Hz), 5.80 (d, 1H, H-2', J=5.8 Hz), 5.70 (d, 1H, H-3') 4.90 (m, 1H, H-4'), 4.35 (m, 2H, H-5, H-5').

Reagent

Benzoyl chloride: Fluka, p.a., ref 12930

3',5'-di-O-Benzoyl-2'-chloro-2'-deoxy-β,L-uridine (4)

To a solution of compound 3 (60.3 g, 0.139 mol) in dimethylformamide (460 ml) was added at 0° C. a 3.2 N-HCl/DMF solution (208 ml, prepared in situ by adding 47.2 ml of acetyl chloride at 0° C. to a solution of 27.3 ml of methanol and 133.5 ml of dimethylformamide). The reaction mixture was stirred at 100° C. for Ih under exclusion of atmospheric moisture, cooled down, and poured into water (4000 ml). The precipitate of compound 4 was collected with suction, washed with water, and recrystallised from ethanol. The crystals were collected, washed with cold ethanol and ether, and dried under diminished pressure. Yield, 60.6 g (92.6%) of compound 4, m.p. 164–165° C.; ^1H NMR (DMSO-d_6) δ ppm 8.7 (br s, 1H, NH), 8.1–7.3 (m, 11H, C_6H_5CO, H-6), 6.15 (d, 1H, H-1', J=4.8 Hz), 5.5 (m, 2H, H-5, H-2'), 4.65 (m, 4H, H-3', H-4', H-5', H-5").

Reagent

Acetyl chloride: Fluka, p.a., ref 00990

3',5'-di-O-Benzoyl-2'-deoxy-β,L-uridine (5)

A mixture of compound 4 (60.28 g, 0.128 mol), tri-n-butyltin hydride (95 ml) and azabisisobutyronitrile (0.568 g) in dry toluene (720 ml) was refluxed under stirring for 5 h and cooled down. The solid was collected with suction and washed with cold toluene and petroleum ether. The filtrate was concentrated under reduced pressure and diluted with petroleum ether to deposit an additional crop of compound 5. Yield, 54.28 g (97.2%) of compound 5; m.p. 220–221° C.; ^1H NMR ($CDCl_3$) δ ppm 8.91 (br s, 1H, NH), 8.1–7.5 (m, 11H, C_6H_5CO and H-6), 6.43 (q, 1H, H-1', $J_{1',2'}$=5.7 Hz and $J_{1',2''}$=8.3 Hz), 5.7–5.6 (m, 2H, H-3' and H-5), 4.8–4.6 (m, 3H, H-5', H-5" and H-4'), 2.8–2.7 (m, 1H, H-2'), 2.4–2.3 (m, 1H, H-2").

Reagents

Tri-n-butyltin hydride: Fluka, >98%, ref 90915

Azabisisobutyronitrile: Fluka, >98%, ref 11630

3',5'-di-O-Benzoyl-2'-deoxy-β-L-4-thio-uridine (6)

A solution of compound 5 (69 g, 0.158 mol) and Lawesson's reagent (74 g) in anhydrous methylene chloride (3900 ml) was refluxed under argon overnight. After evaporation of the solvant, the crude residue was purified by a silica gel column chromatography [eluant: gradient of methanol (0–2%) in methylene chloride] to afford pure compound 6 (73 g) in quantitative yield; ^1H NMR ($CDCl_3$) δ ppm 9.5 (br s, 1H, NH), 8.1–7.4 (m, 10H, C_6H_5CO), 7.32 (d, J=7.7 Hz), 6.30 (dd, 1H, H-1', J=5.6 Hz and J=8.2 Hz), 6.22 (d, 1H,

H-5, J=7.7 Hz), 5.6 (m, 1H, H-3'), 4.7 (m, 2H, H-5', H-5"), 4.5 (m, 1H, H-4'), 2.8 (m, 1H, H-2'), 2.3 (m, 1H, H-2").

Reagent

Lawesson's reagent: Fluka, >98%, ref 61750

2'-Deoxy-β-L-cytosine

A solution of compound 6 (7.3 g, 0.016 mol) in methanol saturated with ammonia (73 ml) was heated at 100° C. in a stainless steel cylinder for 3 h. After cooling carefully, the solvent was evaporated under reduced pressure. An aqueous solution of the residue was washed with ethyl acetate and evaporated to dryness. Such a procedure was carried out on 9 other samples (each 7.3 g) of compound 6 (total amount of 6=73 g). The 10 residues were combined, diluted with absolute ethanol and cooled to give 7 as crystals. Trace of benzamide were eliminated from the crystals of 6 by a solid-liquid extraction procedure (at reflux in ethyl acetate for 1 h). Yield, 28.75 g (78.6%) of compound 6; m. p. 141–145° C.; ^{1}H NMR (DMSO) δ ppm 8.22 and 8.00 (2 br s, 2H, NH_2), 7.98 (d, 1H, H-6, J=7.59 Hz), 6.12 (t, 1H, H-1', J=6.5 Hz and J=7.6 Hz), 5.89 (d, 1H, H-5, J=7.59 Hz), 5.3 (br s, 1H, OH-3'), 5.1 (br s, 1H, OH-5'), 4.2 (m, 1H, H-3'), 3.80 (q, 1H, H-4', J=3.6 Hz and J=6.9 Hz), 3.6–3.5 (m, 2H, H-5', H-5"), 2.2–2.0 (m, 2H, H-2"); FAB<0, (GT) m/e 226 $(M-H)^-$, 110 $(B)^-$; FAB>0 (GT) 228 $(M+H)^+$, 112 $(B+2H)^+$; $[\alpha]_D^{20}$ −56.48 (c=1.08 in DMSO); UV (pH 7) λ_{max}=270 mm (ε=10000).

Reagent

Methanolic Ammonia: previously saturated at −5° C. tightly stoppered, and kept in a freezer.

EXAMPLE 5

Stereoselective Synthesis of 2'-Deoxy-β-L-Thymidine (β-L-dT)

3',5'-di-O-Benzoyl-2'-deoxy-5-iodo-β-L-uridine (z)

A mixture of compound 5 (105.8 g, 0.242 mol), iodine (76.8 g), CAN (66.4 g) and acetonitrile (2550 ml) was stirred at 80° C. for 3 h then the reaction mixture was cooled at room temperature leading to crystallization of compond 7 (86.6 g, 63.5%); m. p. 192–194° C.; ^{1}H NMR (DMSO) δ ppm. 8.34 (s, 1H, NH), 8.2–7.2 (m, 11H,2 C_6H_5CO, H-6), 6.31 (q, 1H, H-1', J=5.5 Hz and J=8.7 Hz), 5.5 (m, 1H, H-3'), 4.7 (m, 2H, H-5', H-5"), 4.5 (m, 1H, H-4'), 2.7 (m, 1H, H-2'), 2.4 (m, 1H, H-2"); FAB<0, (GT) m/e 561 $(M-H)^-$, 237 $(B)^-$; FAB>0 (GT) 563 $(M+H)^+$; $[\alpha]_D^{20}$+39.05 (c=1.05 in DMSO); UV (EtOH 95) υ_{max}=281 nm (ε=9000), υ_{min}=254 nm (ε=4000), υ_{max}=229 nm (ε=31000); Anal. Calcd for $C_{23}H_{19}N_2O_7$: C, 49.13 H, 3.41 N, 4.98 I, 22.57. Found: C, 49.31 H, 3.53 N, 5.05 I, 22.36.

Reagents

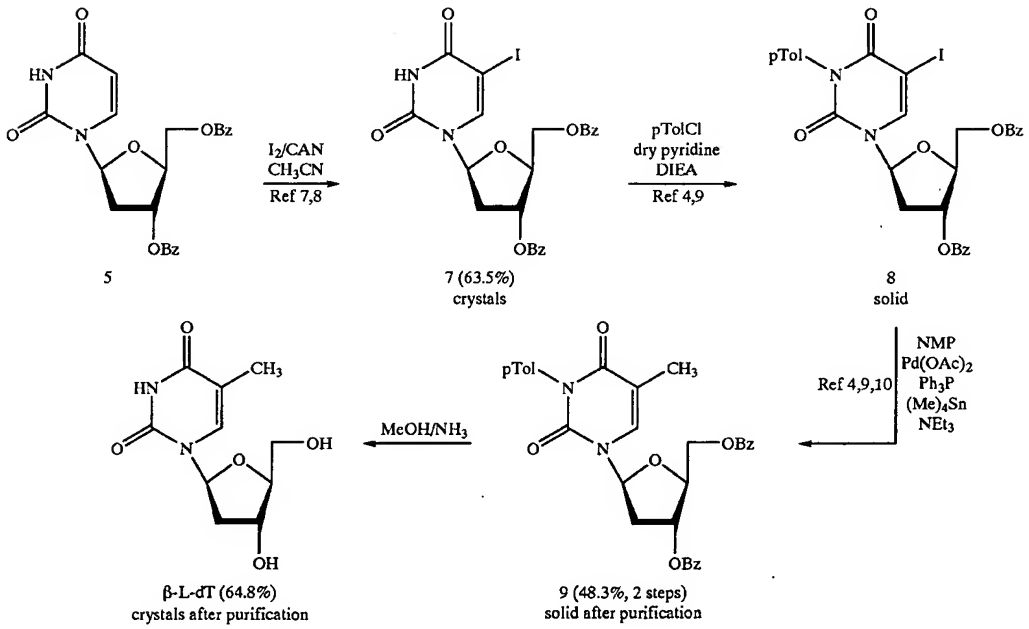
Iodine: Fluka, 99.8%, ref 57650

Cerium ammonium nitrate (CAN): Aldrich, >98.5%, ref 21,547-3

3',5'-di-O-Benzoyl-2'-deoxy-3-N-toluoyl-β-L-thymidine (2)

To a solution of compound 7 (86.6 g, 0.154 mol) in anhydrous pyridine (1530 ml) containing N-ethyldiisopropylanine (53.6 ml) was added, portionwise at 0° C., p-toluoyl chloride (40.6 ml). The reaction mixture was stirred for 2 h at room temperature, then water was added to stop the reaction and the reaction mixture was extracted with methylene chloride. The organic phase was washed with water, dried over sodium sulfate and evaporated to dryness to give crude 3',5'-di-O-benzoyl-2'-deoxy-3-N-toluoyl-5-iodo-β-L-uridine (8) which can be used for the next step without further purification.

A solution of the crude mixture 8, palladium acetate (3.44 g), triphenylphosphine (8.0 g) in N-methylpyrolidinone (1375 ml) with triethylamine (4.3 ml) was stirred at room temperature for 45 min. Then, tetramethyltin (42.4 ml) was added dropwise at 0° C. under argon. After stirring at



100–110° C. overnight, the reaction mixture was poured into water and extracted with diethyl ether. The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography [eluant: stepwise gradient of ethyl acetate (0–10%) in toluene] to give compound 9 as a foam (42.3 g, 48.3% for the 2 steps). ^{1}H NMR (DMSO) δ ppm .8.3–7.2 (m, 15H,2 C_6H_5CO, 1 $CH_3C_6H_4CO$, H-6), 6.29 (t, 1H, H-1', J=7.0 Hz), 5.7 (m, 1H, H-3'), 4.7–4.5 (m, 3H, H-5', H-5", H4'), 2.7–2.6 (m, 2H, H-2', H-2"); FAB<0, (GT) m/e 567 $(M-H)^-$, 449 $(M—CH_3C_6H_4CO)^-$, 243 $(B)^-$, 121 $(C_6H_5COO)^-$; FAB>0 (GT) 1137 $(2M+H)^+$, 569 $(M+H)^+$, 325 $(M-B)^-$, 245 $(B+2H)^+$, 119 $(CH_3C_6H_5CO)^+$.

Reagents

p-Toluoyl chloride, Aldrich, 98%, ref 10,663-1

Diisopropylethylamine: Aldrich, >99.5%, ref 38,764-9

N-methylpyrolidinone: Aldrich, >99%, ref 44,377-8

Paladium acetate: Aldrich, >99.98%, ref 37,987-5

Triphenylphosphine: Fluka, >97%, ref 93092

Tetramethyltin: Aldrich, >99%, ref 14,647-1

2'-Deoxy-β-L-thymidine

A solution of compound 9 (42.3 g, 0.074 mol) in methanol saturated with ammonia (1850 ml) was stirred at room temperature for two days. After evaporation of the solvent, the residue was diluted with water and washed several times with ethyl acetate. The aqueous layer was separated, evaporated under reduced pressure and the residue was purified by a silica gel column chromatography [eluant: stepwise gradient of methanol (0–10%) in methylene chloride] to give pure 2'-deoxy-β-L-thymidine (11.62 g, 64.8%) which was crystallized from ethanol; m.p. 185–188° C.; ^{1}H NMR (DMSO) δ ppm 11.3 (s, 1H, NH), 7.70 (s, 1H, H-6), 6.2 (pt, 1H, H-1'), 5.24 (d, 1H, OH-3', J=4.2 Hz), 5.08 (t, 1H, OH-5', J=5.1 Hz), 4.2 (m, 1H, H-3'), 3.7 (m, 1H, H-4'), 3.5–3.6 (m, 2H, H-5', H-5"), 2.1–2.0 (m, 2H, H-2', H-2"); FAB<0, (GT) m/e 483 $(2M-H)^-$, 349 $(M+T-H)^-$, 241 $(M-H)^-$, 125 $(B)^-$; FAB>0 (GT) 243 $(M+H)^+$, 127 $(B+2H)^+$; $[\alpha]_D^{20}$–13.0 (c=1.0 in DMSO); UV (pH 1) υ_{max}=267 nm (ε=9700), υ_{min}=234 nm (ε=2000).

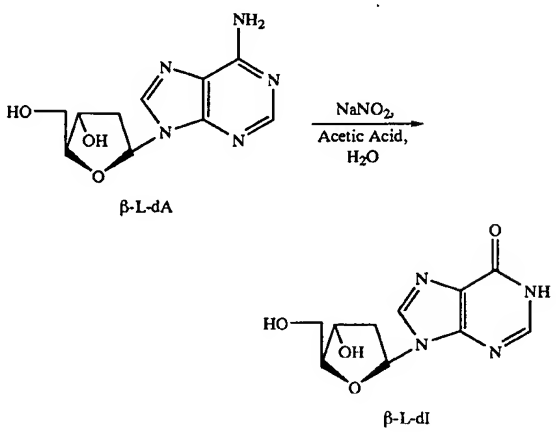
Reagent

Methanolic ammonia: previously saturated at -5° C., tightly stoppered, and kept in a freezer.

EXAMPLE 6

Stereoselective Synthesis of 21-deoxy-pLnosine (β-L-dI)

β-L-dI was synthesized by deamination of 2'-deoxy-β-L-adenosine (P-LdA) following a procedure previously described in the 9-D-glucopyranosyl series (Ref: I. Iwai, T. Nishimura and B. Shimizu, Synthetic Procedures in Nucleic Acid Chemistry, W. W. Aorbach and R. S. Tipson, eds., John Wiley & Sons, Inc. New York, vol. 1, pp. 135–138 (1968)).



Thus, a solution of β-L-DA (200 mg) in a mixture of acetic acid (0.61 ml) and water (19 ml) was heated with sodium nitrite (495 mg), and the mixture was stirred at room temperature overnight. The solution was then evaporated to dryness under diminished pressure. An aqueous solution of the residue was applied to a column of IR-120 (H^+) ion-exchange resin, and the column was eluted with water. Appropriate fractions were collected and evaporated to dryness to afford pure β-L-dI which was crystallized from methanol (106 mg, 53% yield not optimized): m.p.= 209°–211° C.; UV (H_2O), λ_{max}=247 nm; ^{1}H-NMR (DMSO-d_6)=8.32 and 8.07 (2s, each, H-2 and H-8), 6.32 (pt, 1H, H-1; J=6.7 Hz), 4.4 (m, 1H, H-3'), 3.9 (m, 1H, H-4'), 3.7–3.4 (m, 2H partially obscured by HOD, H-5',5"), 2.6 and 2.3 (2m, 1H each, H-2' and H-2"); mass spectra (mature, glycerol-thioglycerol, 1:1, v/v), FAB>0: 253 $(m+H)^+$, 137 (base +2H)$^+$; FAB<0: 251 $(m-H)^-$, 135 (base); $[\alpha]_D^{20}$=+ 19.3 (-c 0.88, H_2O).

Anti-HBV Activity of the Active Compounds

The ability of the active compounds to inhibit the growth of virus in 2.2.15 cell cultures (HepG2 cells transformed with hepatitis virion) can be evaluated as described in detail below.

A summary and description of the assay for antiviral effects in this culture system and the analysis of HBV DNA has been described (Korba and Milman, 1991, *Antiviral Res.*, 15:217). The antiviral evaluations are performed on two separate passages of cells. All wells, in all plates, are seeded at the same density and at the same time.

Due to the inherent variations in the levels of both intracellular and extracellular HBV DNA, only depressions greater than 3.5-fold (for HBV virion DNA) or 3.0-fold (for HBV DNA replication intermediates) from the average levels for these HBV DNA forms in untreated cells are considered to be statistically significant (P<0.05). The levels of integrated HBV DNA in each cellular DNA preparation (which remain constant on a per cell basis in these experiments) are used to calculate the levels of intracellular HBV DNA forms, thereby ensuring that equal amounts of cellular DNA are compared between separate samples.

Typical values for extracellular HBV virion DNA in untreated cells range from 50 to 150 pg/ml culture medium (average of approximately 76 pg/ml). Intracellular HBV DNA replication intermediates in untreated cells range from 50 to 100 μg/pg cell DNA (average approximately 74 pg/μg cell DNA). In general, depressions in the levels of intrac-

ellular HBV DNA due to treatment with antiviral compounds are less pronounced, and occur more slowly, than depressions in the levels of HBV virion DNA (Korba and Milman, 1991, *Antiviral Res.*, 15:217).

The manner in which the hybridization analyses are performed for these experiments result in an equivalence of approximately 1.0 pg of intracellular HBV DNA to 2–3 genomic copies per cell and 1.0 pg/ml of extracellular HBV DNA to 3×10^5 viral particles/ml.

EXAMPLE 7

The ability of the triphosphate derivatives of β-L-dA, β-L-dC, β-L-dU, β-L-2'-dG, β-L-dI, and β-L-dT to inhibit hepatitis B was tested. Table 1 describes the comparative inhibitory activities of triphosphates of β-L-dT (β-L-dT-TP), β-L-dC (β-L-dC-TP), β-L-dU (β-L-dU-TP) and β-L-dA (β-L-dA-TP) on woodchuck hepatitis virus (WHV) DNA polymerase, human DNA polymerases α, β, and γ.

TABLE 1

Inhibitor	WHV DNA pol IC_{50}	DNA pol α K_i[b] (μM)	DNA pol β K_i[b] (μM)	DNA pol γ K_i[b] (μM)
β-L-dT-TP	0.34	>100	>100	>100
β-L-dA-TP	2.3	>100	>100	>100
β-L-dC-TP	2.0	>100	>100	>100
β-L-dU-TP	8	>100	>100	>100

[a]IC_{50}: 50% Inhibitory concentration
[b]K_i value was determined using calf thymus activated DNA as template-primer and dATP as substrate. Inhibitors were analyzed by Dixon plot analysis. Under these conditions, the calculated mean K_m of human DNA polymerase α for dATP as approximately 2.6 μM. Human DNA polymerase β exhibited a steady state K_m of 3.33 μM for dATP. Human DNA polymerase γ exhibited a steady K_m of 5.2 μM.

EXAMPLE 8

The anti-hepatitis B virus activity of β-L-dA, β-L-dC, β-L-dU, β-L-2'-dG and β-L-DT was tested in transfected Hep G-2 (2.2.15) cells. Table 2 illustrates the effect of β-L-dA, β-L-dC, β-L-dU, and β-t-dT against hepatitis B virus replication in transfected Hep G-2 (2.2.15) cells.

TABLE 2

Compound	HBV virions[a] EC_{50} (μM)	HBV Ri[b] EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	Selectivity Index IC_{50}/EC_{50}
β-L-dT	0.05	0.05	>200	>4000
β-L-dC	0.05	0.05	>200	>4000
β-L-dA	0.10	0.10	>200	>2000
β-L-dI	1.0	1.0	>200	>200
β-L-dU	5.0	5.0	>200	>40

[a]Extracellular DNA
[b]Replicative intermediates (Intracellular DNA)

EXAMPLE 9

The effect of β-L-dA, β-L-dC and β-L-dT in combination on the growth of hepatitis B was measured in 2.2.15 cells. The results are provided in Table 3.

TABLE 3

Combination	Ratio	EC_{50}
L-dC + L-dT	1:3	.023
L-dC + L-dT	1:1	.053
L-dC + L-dT	3:1	.039
L-dC + L-dA	1:30	.022
L-dC + L-dA	1:10	.041
L-dC + L-dA	1:3	.075
L-dT + L-dA	1:30	.054
L-dT + L-dA	1:10	.077
L-dT + L-dA	1:3	.035

Each combination produced anti-HBV activity that was synergistic. In addition, the combination of L-dA+L-dC+L-dT was also synergistic in this model.

EXAMPLE 10

The inhibition of hepatitis B replication in 2.2.15 cells by β-L-DA and β-L-dC, alone and in combination was measured. The results are shown in Table 4.

TABLE 4

[a]β-L-2'-deoxy-adenosine (μM)	[b]β-L-2'-deoxy-cytidine (μM)	% Inhibition	[c]C.I.
0.5		90	
0.05		24	
0.005		1	
	0.5	95	
	0.05	40	
	0.005	10	
0.05	0.05	80	0.34
0.05	0.005	56	0.20
0.05	0.0005	50	0.56
0.005	0.05	72	0.35
0.005	0.005	54	0.35
0.005	0.0005	30	0.16
0.0005	0.05	50	0.83
0.0005	0.005	15	0.28
0.0005	0.0005	0	N.A.

[a]β-L-2'-deoxy-adenosine: IC_{50} = 0.09 μM
[b]β-L-2'-deoxy-cytidine: IC_{50} = 0.06 μM
[c]Combination indices values indicate synergism effect (<1), additive effect (=1), and antagonism effect (>1)

EXAMPLE 11

The efficacy of L-dA, L-dT and L-dC against hepadnavirus infection in woodchucks (*Marmota monax*) chronically infected with woodchuck hepatitis virus (WHV) was determined. This animal model of HBV infection is widely accepted and has proven to be useful for the evaluation of antiviral agents directed against HBV.

Protocol:

Experimental groups (n=3 animals/drug group, n=4 animals/control)

Group 1	vehicle control
Group 2	lamivudine (3TC) (10 mg/kg/day)
Groups 3–6	L-dA (0.01, 0.1, 1.0, 10 mg/kg/day)
Groups 7–10	L-dT (0.01, 0.1, 1.0, 10 mg/kg/day)
Groups 11–14	L-dC (0.01, 0.1, 1.0, 10 mg/kg/day)

Drugs were administered by oral gavage once daily, and blood samples taken on days 0, 1, 3, 7, 14, 21, 28, and on post-treatment days +1, +3, +7, +14, +28 and +56. Assessment of the activity and toxicity was based on the reduction of WHV DNA in serum: dot-blot, quantative PCR.

The results are illustrated in FIG. 3 and Table 5.

TABLE 5

Antiviral Activity of LdA, LdT, LdC in Woodchuck Model of Chronic HBV Infection

	Control	LdA	LdT	LdC
day	ng WHV-DNA per ml serum[1, 2]			
0	381	436	423	426
1	398	369	45	123
3	412	140	14	62
7	446	102	6	46
14	392	74	1	20

[1]LdA, LdT, LdC administered orally once a day at 10 mg/kg
[2]limit of detection is 1 ng/ml WHV-DNA per ml serum

The data show that L-dA, L-dT and L-dC are highly active in this in vivo model. First, viral load is reduced to undetectable (L-dT) or nearly undetectable (L-dA, L-dC) levels. Second, L-dA, L-dT and L-dC are shown to be more active than 3TC (lamivudine) in this model. Third, viral load is not detected for at least two weeks after withdrawal of L-dT. Fourth, dose response curves suggest that a modes increase in the dose of L-dA and L-dC would show antivity similar to L-dT. Fifth, all animals receiving the drugs gained weight and no drug-related toxicity was detected.

Toxicity of Compounds

Toxicity analyses were performed to assess whether any observed antiviral effects are due to a general effect on cell viability. The method used is the measurement of the effect of β-L-dC and β-L-dT on cell growth in human bone marrow clorogenic assays, as compared to Lamuvidine. The results are provided in Table 6.

TABLE 6

Compound	CFU-GM (μM)	BFU-E (μM)
β-L-dA	>10	>10
β-L-dC	>10	>10
β-L-dT	>10	>10
β-L-dU	>10	>10
Lamuvidine	>10	>10

Preparation of Pharmaceutical Compositions

Humans suffering from any of the disorders described herein, including hepatitis B, can be treated by administering to the patient an effective amount of a β-2'-deoxy-β-L-erythro-pentofuranonucleoside, for example, β-L-2'-deoxyadenosine, β-L-2'-deoxycytidine, β-L-2'-deoxyuridine, β-L-2'-deoxyguanosine or β-L-2'-deoxythymidine or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, without causing serious toxic effects in the patient treated. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein.

A preferred dose of the compound for all of the above-mentioned conditions will be in the range from about 1 to 50 mg/kg, preferably 1 to 20 mg/kg, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable prodrug can be calculated based on the weight of the parent nucleoside to be delivered. If the prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg, preferably 70 to 1400 mg of active ingredient per unit dosage form. A oral dosage of 50–1000 mg is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to 70 μM, preferably about 1.0 to 10 μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable derivative or salts thereof can also be mixed with other active

materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, protease inhibitors, or other nucleoside or nonnucleoside antiviral agents. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

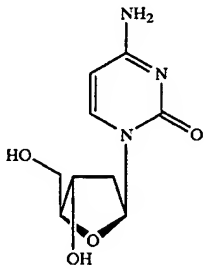
In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylacetic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention. It is intended that all of these variations and modifications be included within the scope of the this invention.

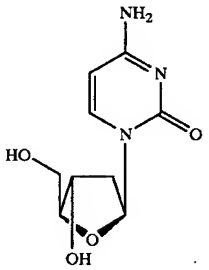
We claim:

1. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



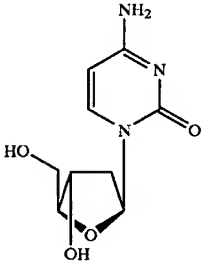
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), or pharmaceutically acceptable salt thereof.

2. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



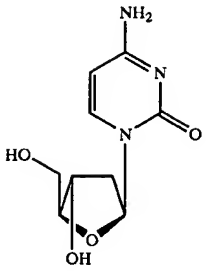
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), or pharmaceutically acceptable salt thereof.

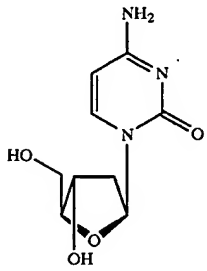
3. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine (L-FMAU), or pharmaceutically acceptable salt thereof.

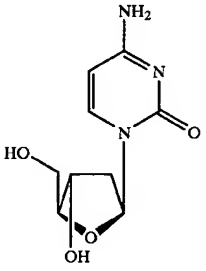
4. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:





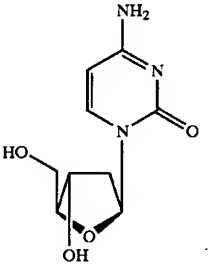
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-D-2,6-diaminopurine dioxolane (DAPD), or pharmaceutically acceptable salt thereof.

5. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of famciclovir, or pharmaceutically acceptable salt thereof.

6. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:

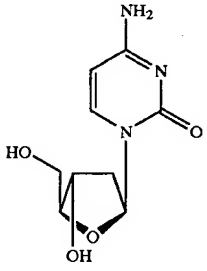


or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of penciclovir, or pharmaceutically acceptable salt thereof.

7. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:

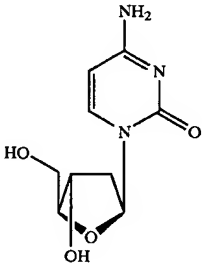
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), or pharmaceutically acceptable salt thereof.

8. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



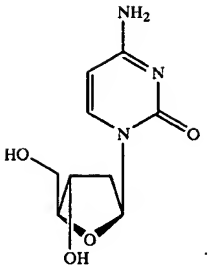
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 9-[2-(phosphono-methoxy)ethyl]adenine (PMEA, adefovir, dipivoxil), or pharmaceutically acceptable salt thereof.

9. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



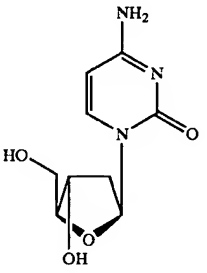
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of lobucavir, or pharmaceutically acceptable salt thereof.

10. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



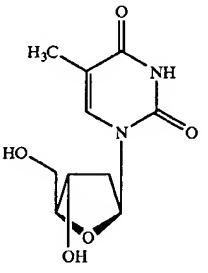
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ganciclovir, or pharmaceutically acceptable salt thereof.

11. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



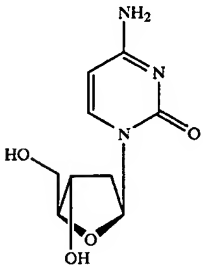
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ribavirin, or pharmaceutically acceptable salt thereof.

12. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



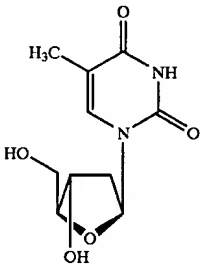
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), or pharmaceutically acceptable salt thereof.

13. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-2'-deoxycytidine of the formula:



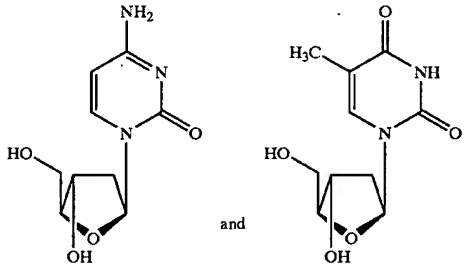
or pharmaceutically acceptable salt thereof.

14. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of β-L-thymidine of the formula:



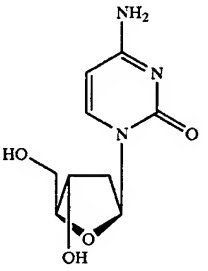
or pharmaceutically acceptable salt thereof.

15. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a combination of the following nucleosides:



or pharmaceutically acceptable salt thereof.

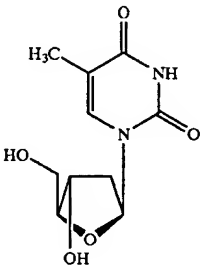
16. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), cis-2-

hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

17. A method the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of a compound selected from the group consisting of β-L-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine (L-FMAU), β-D-2,6-diaminopurine dioxolane (DAPD), famciclovir, penciclovir, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA, adefovir, dipivoxil); lobucavir, ganciclovir and ribavirin.

18. The method of claim **13**, wherein the β-L-2'-deoxycytidine is at least 95% in its designated enantiomeric form.

19. The method of claim **13**, wherein the β-L-2'-deoxycytidine is administered in a pharmaceutically acceptable carrier.

20. The method of claim **19**, wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

21. The method of claim **19**, wherein the pharmaceutically acceptable carrier is suitable for intravenous delivery.

22. The method of claim **19**, wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

23. The method of claim **19**, wherein the pharmaceutically acceptable carrier is suitable for intradermal delivery.

24. The method of claim **19**, wherein the pharmaceutically acceptable carrier is suitable for subcutaneous deliery.

25. The method of claim **19**, wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

26. The method of claim **19**, wherein the compound is in the form of a dosage unit.

27. The method of claim **26**, wherein the dosage unit contains 10 to 1500 mg of the compound.

28. The method of claim **26** or **27**, wherein the dosage unit is a tablet or capsule.

29. The method of claim **14**, wherein the β-L-thymidine is at least 95% in its designated enantiomeric form.

30. The method of claim **14**, wherein the β-L-thymidine is administered in a pharmaceutically acceptable carrier.

31. The method of claim **29**, wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

32. The method of claim **29**, wherein the pharmaceutically acceptable carrier is suitable for intravenous delivery.

33. The method of claim **29**, wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

34. The method of claim **29**, wherein the pharmaceutically acceptable carrier is suitable for intradermnal delivery.

35. The method of claim **29**, wherein the pharmaceutically acceptable carrier is suitable for subcutaneous delivery.

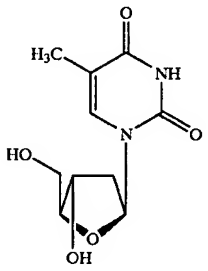
36. The method of claim **29**, wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

37. The method of claim **29**, wherein the compound is in the form of a dosage unit.

38. The method of claim **37**, wherein the dosage unit contains 10 to 1500 mg of the compound.

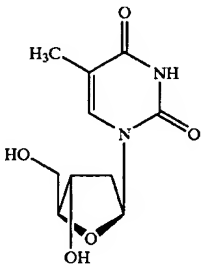
39. The method of claim **37** or **38**, wherein the dosage unit is a tablet or capsule.

40. A method for the treatment of a heptitis B virus infection in a human compriding administering an effective amount of a compound of the formula:



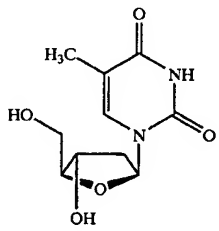
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), or pharmaceutically acceptable salt thereof.

41. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-L-2'-fluoro-5-methyl-arabinofuranosyl-uridine (L-FMAU), or pharmaceutically acceptable salt thereof.

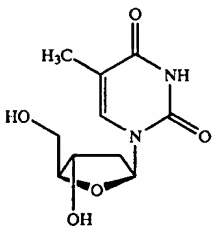
42. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of β-D-2,6-

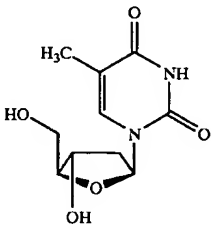
diaminopurine dioxolane (DAPD), or pharmaceutically acceptable salt thereof.

43. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



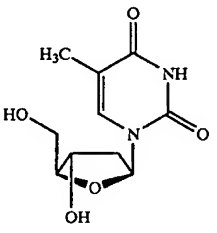
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of famciclovir, or pharmaceutically acceptable salt thereof.

44. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



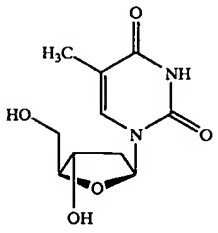
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of penciclovir, or pharmaceutically acceptable salt thereof.

45. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



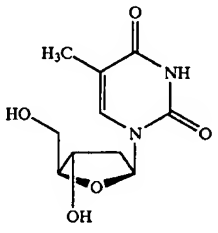
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylene-cyclopentyl]-6H-purin-6-one (entecavir, BMS-200475), or pharmaceutically acceptable salt thereof.

46. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



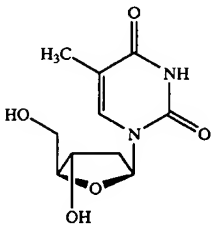
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA, adefovir, dipivoxil), or pharmaceutically acceptable salt thereof.

47. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



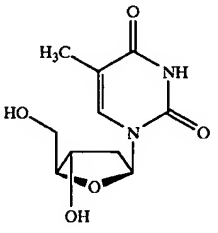
or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of lobucavir, or pharmaceutically acceptable salt thereof.

48. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ganciclovir, or pharmaceutically acceptable salt thereof.

49. A method for the treatment of a hepatitis B virus infection in a human comprising administering an effective amount of a compound of the formula:



or pharmaceutically acceptable salt thereof, in combination or alternation with an effective amount of ribavirin, or pharmaceutically acceptable salt thereof.

* * * * *

Exhibit 6

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DECEMBER 16, 1999

PTAS

101159234A

SHERRY M. KNOWLES, ESQ.
191 PEACHTREE STREET
ATLANTA, GEORGIA 30303-1763

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 09/27/1999

REEL/FRAME: 010271/0725
NUMBER OF PAGES: 8

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
GOSSELIN, GILLES

DOC DATE: 08/20/1999

ASSIGNOR:
IMBACH, JEAN-LOUIS

DOC DATE: 08/20/1999

ASSIGNOR:
BRYANT, MARTIN

DOC DATE: 09/03/1999

ASSIGNEE:
NOVIRIO PHARMACEUTICALS LIMITED
C/O WALER STREET, WALKER HOUSE
GRAND CAYMAN, CAYMAN ISLANDS

ASSIGNEE:
CENTRE NATIONAL DA LA RECHERCHE
SCIENTIFIQUE
3, RUE MICHEL-ANGE
75794, PARIS, CEDEX 16, FRANCE

Docket No. 06171.105005 US
Attorney SMK
Due Date NDD
Date Docketed 1/7/2000 jnvt

SERIAL NUMBER: 60131352 FILING DATE: 04/28/1999
PATENT NUMBER: ISSUE DATE:

SERIAL NUMBER: 60096110 FILING DATE: 08/10/1998
PATENT NUMBER: ISSUE DATE:

SERIAL NUMBER: 09371747 FILING DATE: 08/10/1999
PATENT NUMBER: ISSUE DATE:

KIMBERLY WHITE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

AUTHORIZATION TO CHARGE ADDITIONAL FEES TO DEPOSIT ACCOUNT

DECEMBER 16, 1999

TO: OFFICE OF FINANCE

FROM: ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

SUBJECT: DEPOSIT ACCOUNT CHARGE(S)

CHARGE THE DEPOSIT ACCOUNT LISTED BELOW ADDITIONAL FEE(S) AS INDICATED BELOW. AUTHORIZATION TO CHARGE ADDITIONAL FEES HAS BEEN PROVIDED PER THE ATTACHED COVER SHEET, OR BY DIRECT CONTACT WITH THE CUSTOMER.

DEPOSIT ACCOUNT NUMBER: 110980
PROPERTY NUMBER: 60131352

RECORDING FEES:

FEE CODE: 581 AMOUNT: 40

IF YOU HAVE ANY QUESTIONS REGARDING THIS NOTICE, YOU MAY CONTACT THE INDIVIDUAL WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723.

KIMBERLY WHITE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

TRADEMARK SERVICE FEES:	FEE CODE:
RECORDING FIRST MARK	481
RECORDATION SECOND AND SUBSEQUENT MARK IN SAME DOCUMENT	482
LABOR CHARGES FOR SERVICES PER HOURS OR FRACTION THEREOF	484
UNSPECIFIED OTHER SERVICES	485

PATENT SERVICE FEES:

RECORDING EACH PATENT ASSIGNMENT,	581

AGREEMENT, OTHER PAPER, PER PROPERTY	
LABOR CHARGES FOR SERVICES PER HOUR ($30) OR FRACTION THEREOF	584
UNSPECIFIED OTHER SERVICES	585

10-01-1999

101159234

FORM-PTO-1595 TRANSM[illegible]ATION
1-31-92 9.27.99

Atty. Docket 06171.105005

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): Gilles Gosselin, Jean-Louis Imbach, And Martin Bryant

Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Novirio Pharmaceuticals Limited
Foreign Address: c/o Walker Secretaries
Walker House
Grand Cayman, Cayman Islands

Domestic Address:

City:____ State:_____ZIP:_____

Additional name(s) & address(es) attached?
☒ Yes ☐ No

3. Nature of Conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
Other _____
Execution Date: 8/20/99, 8/20/99, and 9/3/99

4. Application number (s) or patent numbers(s):
If this document is being filed together with a new application, the execution date of the application is: 6/24/99

A. Patent Application No.(s) 60/131,352, 60/096,110 and 09/371,747

B Patent Registration No. (s)

Additional numbers attached ? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Sherry M. Knowles, Esq.
191 Peachtree Street
Atlanta, Georgia 30303-1763
Telephone No.: 404- 572- 4600
Facsimile No.: 404 572-5100

6. Number of applications and patents involved:
three

7. Total fee (37 CFR 3.41): $ 80
☒ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number
11-0980
(Attach duplicate copy of this page if paying by deposit account):

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy of the original document.

Jacqueline Haley — Jacqueline Haley — September 22, 1999

Name of Person Signing — Signature — Date

Total number of pages comprising cover sheet: 2

Second Applicant:

Centre National Da La Recherche Scientifique
3, Rue Michel-ange
75794, Paris, cedex 16, France

ASSIGNMENT

WHEREAS, WE, GILLES GOSSELIN, JEAN-LOUIS IMBACH, AND MARTIN BRYANT have invented certain improvements in "β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B" for which we have executed United States provisional application nos. 60/131,352 and 60/096,110 which were filed on April 28, 1999 and August 10, 1998 respectively; and U.S. Application No. 09/371,747 which was filed on August 10, 1999 and

WHEREAS, NOVIRIO PHARMACEUTICALS LIMITED, a Cayman Island corporation having an office at c/o Walker Secretaries, Walker House, Grand Cayman, Cayman Islands desires to purchase same;

NOW, THEREFORE, in consideration of the sum of Five Dollars ($5.00) and other good and valuable consideration paid by NOVIRIO PHARMACEUTICALS, LIMITED, the receipt and sufficiency of which are hereby acknowledged, I, MARTIN BRYANT, have sold, assigned, transferred and conveyed and by these presents do hereby sell, assign, transfer and convey unto NOVIRIO PHARMACEUTICALS, LIMITED, in and for the United States and its territories and for foreign countries, the entire right, title and interest in and to said provisional application and said application for United States Letters Patent, in and to the invention therein set forth and in and to any patent which may issue on said provisional applications for United States Letters Patent or any application, reissue, renewal, division, continuation or continuation-in-part thereof; and I hereby bind myself, my heirs, legal representatives, administrators and assigns properly to execute without further consideration, any and all applications, petitions, oaths and assignments or other papers and instruments which may be necessary in order to carry into full force and effect the sale, assignment, transfer and conveyance hereby made or intended to be made.

IN WITNESS WHEREOF, I have hereunto set my hand and seal this 3 day of September, 1999.

MARTIN BRYANT

STATE OF Massachusetts)
) ss.
COUNTY OF)

On this 3rd day of September, 1999, before me, a notary public, came MARTIN BRYANT, to me known and known to be the individual described in and who executed the foregoing assignment, and he duly acknowledged the same to be his free act and deed.

Notary Public

(SEAL)

My commission expires: 2/17/06

06171.105005

ASSIGNMENT

WHEREAS, WE, GILLES GOSSELIN, JEAN-LOUIS IMBACH, AND MARTIN BRYANT have invented certain improvements in "β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B" for which we have executed United States provisional application nos. 60/131,352 and 60/096,110 which were filed on April 28, 1999 and August 10, 1998 respectively; and U.S. Application No. 09/371,747 which was filed on August 10, 1999 and

WHEREAS, Centre National Da La Recherche Scienrifique (CNRS), a public agency operating under the supervisory authority of France's Ministry of Research and Technology, located at 3, Rue Michel-ange 75794, Paris, cedex 16, France desires to purchase same;

NOW, THEREFORE, in consideration of the sum of Five Dollars ($5.00) and other good and valuable consideration paid by Centre National Da La Recherche Scientifique , the receipt and sufficiency of which are hereby acknowledged, I, GILLES GOSSELIN, have sold, assigned, transferred and conveyed and by these presents do hereby sell, assign, transfer and convey unto Centre National Da La Recherche Scientifique , in and for the United States and its territories and for foreign countries, the entire right, title and interest in and to said provisional application and said application for United States Letters Patent, in and to the invention therein set forth and in and to any patent which may issue on said provisional applications for United States Letters Patent or any application, reissue, renewal, division, continuation or continuation-in-part thereof; and I hereby bind myself, my heirs, legal representatives, administrators and assigns properly to execute without further consideration, any and all applications, petitions, oaths and assignments or other papers and instruments which may be necessary in order to carry into full force and effect the sale, assignment, transfer and conveyance hereby made or intended to be made.

IN WITNESS WHEREOF, I have hereunto set my hand and seal this 20 day of August, 1999.

GILLES GOSSELIN

On this 20 day of August, 1999, before me, a notary public, came Gilles Gosselin, to me known and known to be the individual described in and who executed the foregoing assignment, and he duly acknowledged the same to be his free act and deed.

Notary Public

(SEAL)

My commission expires:_____

Me Vincent CAPELA-LABORDE, Notaire associé, MONTPELLIER (Hlt) COUR D'APPEL
RÉPUBLIQUE FRANÇAISE

Société Civile Professionnelle
André SIMONNET
Philippe OLIVIER
Vincent CAPELA-LABORDE
Notaires Associés
14, Rue Foch - B.P. 2082
34025 MONTPELLIER Cedex 1

06171.105005

ASSIGNMENT

WHEREAS, WE, GILLES GOSSELIN, JEAN-LOUIS IMBACH, AND MARTIN BRYANT have invented certain improvements in "β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B" for which we have executed United States provisional application nos. 60/131,352 and 60/096,110 which were filed on April 28, 1999 and August 10, 1998 respectively; and U.S. Application No. 09/371,747 which was filed on August 10, 1999 and

WHEREAS, Centre National Da La Recherche Scientifique (CNRS) a public agency operating under the supervisory authority of France's Ministry of Research and Technology, located at 3, Rue Michel-ange 75794, Paris, cedex 16, France desires to purchase same;

NOW, THEREFORE, in consideration of the sum of Five Dollars ($5.00) and other good and valuable consideration paid by Centre National Da La Recherche Scienrifique , the receipt and sufficiency of which are hereby acknowledged, I, JEAN-LOUIS IMBACH, have sold, assigned, transferred and conveyed and by these presents do hereby sell, assign, transfer and convey unto Centre National Da La Recherche Scientifique , in and for the United States and its territories and for foreign countries, the entire right, title and interest in and to said provisional application and said application for United States Letters Patent, in and to the invention therein set forth and in and to any patent which may issue on said provisional applications for United States Letters Patent or any application, reissue, renewal, division, continuation or continuation-in-part thereof; and I hereby bind myself, my heirs, legal representatives, administrators and assigns properly to execute without further consideration, any and all applications, petitions, oaths and assignments or other papers and instruments which may be necessary in order to carry into full force and effect the sale, assignment, transfer and conveyance hereby made or intended to be made.

to be made.

IN WITNESS WHEREOF, I have hereunto set my hand and seal this 20 day of August, 1999.

JEAN-LOUIS IMBACH

On this 20 day of August, 1999, before me, a notary public, came Jean-Louis Imbach, to me known and known to be the individual described in and who executed the foregoing assignment, and he duly acknowledged the same to be his free act and deed.

Notary Public

(SEAL)

My commission expires:_____

Me Vincent CAPELA-LABORDE, Notaire associé, MONTPELLIER (Hll) COUR D'APPEL
RÉPUBLIQUE FRANÇAISE

Société Civile Professionnelle
André SIMONNET
Philippe OLIVIER
Vincent CAPELA-LABORDE
Notaires Associés
14, Rue Foch - B.P. 2082
34025 MONTPELLIER Cedex 1

06171.105005

UNITED STATES
PATENT AND
TRADEMARK OFFICE

06171.105005

AUGUST 01, 2002

PTAS

Chief Information Officer
Washington, DC 20231
www.uspto.gov

KING & SPALDING
SHERRY M. KNOWLES
45TH FLOOR, 191 PEACHTREE STREET, N.E.
ATLANTA, GA 30303

102111599A

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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 06/03/2002

REEL/FRAME: 012937/0346
NUMBER OF PAGES: 7

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS)

DOC DATE: 04/19/2002

ASSIGNEE:
L'UNIVERSITE MONTPELLIER II (UMII)
2 PLACE EUGENE BATAILLON 34095
MONTPELLIER CEDEX 5,, FRANCE

SERIAL NUMBER: 09371747
PATENT NUMBER: 6395716

FILING DATE: 08/10/1999
ISSUE DATE: 05/28/2002

SERIAL NUMBER: 09459150
PATENT NUMBER:

FILING DATE: 12/10/1999
ISSUE DATE:

SERIAL NUMBER: 10022276
PATENT NUMBER:

FILING DATE: 12/14/2001
ISSUE DATE:

SERIAL NUMBER: 10022148
PATENT NUMBER:

FILING DATE: 12/14/2001
ISSUE DATE:

SERIAL NUMBER: 09371747
PATENT NUMBER: 6395716

FILING DATE: 08/10/1999
ISSUE DATE: 05/28/2002

STEVEN POST, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

06-05-2002

102111599

Form PTO-1595 (Adapted)
3-13-96

U.S. DEPARTMENT OF COMMERCE
U.S. Patent & Trademark Office

OFFICE OF PUBLIC RECORDS
FINANCE SECTION
JUN -3 AM 9:45

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner for Patents. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): 6-3-02

Centre National De La Recherche Scientifique (CNRS)

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: **L' Université Montpellier II (UMII)**

Address: **2 place Eugéne Bataillon 34095**

City, State, Zip **Montpellier Cedex 5, France**

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment

NOTE: This Assignment conveys only the rights received from Jean-Louis Imbach and is being submitted in English & French along with Attachment A

Execution Date: **April 19, 2002**

4(a). Patent Application No.(s): **09/371,747; 09/459,150; 10/022,276; and 10/022,148**

4(b). Patent No.(s): **6,395,716**

If this document is being filed together with a new application, the execution date of the application is: _____

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: **Sherry M. Knowles**

Address: **KING & SPALDING**
45th Floor, 191 Peachtree Street, N.E.
Atlanta, Georgia 30303

6. Total number of applications and patents involved: **5**

7. Total fee (37 CFR 3.41) enclosed: **$ 40.00 x 5 = $200.00**

DO NOT USE THIS SPACE

8. Statement

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Certificate of Mailing Statement and Signature

I certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Box Assignments, Washington, DC 20231, on the date given below.

Josephine Young — Name of Person Signing

Signature

5/24/02 — Date

Attorney Docket No: **06171.105005 (NOV 1000)**

Total number of pages including cover sheet: **7**

Mail documents to be recorded with required cover sheet information to:

Commissioner for Patents
Box Assignments
Washington, DC 20231

06/04/2002 TDIAZ1 00000177 09371747
01 FC:581 200.00 OP

ASSIGNMENT

THIS ASSIGNMENT, made by Centre National De La Recherche Scientifique (CNRS), a public agency operating under the supervisory authority of France's Ministry of Research and Technology, located at 3, Rue Michel-Ange 75794, Paris, Cedex 16, France, assigns to the L'Université Montpellier II (UMII), a Public Institution with cultural and professional vocation, located at 2 place Eugène Bataillon 34095 Montpellier Cedex 5, all rights received by CNRS from Jean-Louis Imbach by written assignment to the patents and patent applications listed in Attachment A. For avoidance of doubt, it is confirmed that this Assignment does not convey any of the ownership rights of CNRS arising out of the work of Dr. Gilles Gosselin in the patents and patent applications listed in Attachment A, and that the CNRS remains a co-assignee of all of the patents and patent applications listed in Attachment A by virtue of its ownership rights flowing from the work of Dr. Gilles Gosselin.

NOW, THEREFORE, To All Whom It May Concern, be it known that and other good and valuable consideration the receipt and sufficiency of which are hereby acknowledged, the above Assignor has sold and by these presents does hereby sell, assign, transfer and convey unto the said Assignee, and assigns the full title and interest of Jean-Louis Imbach in and to said Patents, in the inventions represented thereby and any and all reissues, renewals, divisions, continuations, and any other applications that claim priority thereto or from which these applications claim priority, letters Patent or continuations-in-part thereof; or any foreign counterpart thereof, and which may be granted therefor or thereon, for the full end of term for which said Letters Patent may be granted, and all applications, petitions, oaths and assignments or other papers and instruments which may be necessary in order to carry into full force and effect the sale, assignment, transfer and conveyance hereby made or intended to be made.

From time to time after the date hereof, at the request of either party hereto, and at the expense of the party so requesting, each of the parties hereto shall execute and deliver to such requesting party such documents and take such other action as such requesting party may reasonably request in order to consummate more effectively the transactions contemplated hereby.

The Assignor further covenants and agrees that, at the time of the execution and delivery of these presents, it possesses full title to the inventions and Patents thereon as earlier identified, and that it has the unencumbered right and authority to make this assignment.

This Assignment has been drafted in the English and French language. In case of contradiction between the two versions, the French language document will prevail.

Centre National de La Recherche Scientifique
Assignor

By _____ Pour le Directeur Général
et par Délégation
Title Le Délégué aux Entreprises par intérim

Joseph BAIXERAS

CESSION

Par le présent contrat, le Centre National de la Recherche Scientifique (CNRS), établissement public agissant sous la tutelle du Ministre français chargé de la Recherche, situé au 3, Rue Michel-Ange, 75794, Paris Cedex 16, France, fait cession à l'Université Montpellier II (UMII), établissement public à caractère scientifique, culturel et professionnel, situé 2 place Eugène Bataillon, 34095 Montpellier Cedex 5, de l'ensemble des droits transférés par Monsieur Jean-Louis Imbach au CNRS en vertu d'un contrat de cession écrit, et afférents aux brevets et aux demandes de brevets listés à l'Annexe A. Il est précisé et confirmé que la présente cession ne porte aucunement sur les droits de propriété du CNRS résultant des travaux menés par le Docteur Gilles Gosselin dans les brevets et les demandes de brevets listés à l'Annexe A, et que le CNRS demeure co-cessionnaire de l'ensemble des brevets et demandes de brevets listés à l'Annexe A en vertu des droits de propriété générés par les travaux du Docteur Gilles Gosselin.

En conséquence de quoi, le Cédant ci-dessus mentionné a cédé et par les présentes cède et transfère au Cessionnaire ci-dessus mentionné l'intégralité des droits de propriété et de jouissance détenus par Monsieur Jean-Louis Imbach sur les dits Brevets, sur les inventions qu'ils représentent, et sur toute délivrance (*"reissues"*), tout renouvellement, tout divisionnaire, toute extension ("*continuation*") et toute autre demande revendiquant priorité sur ceux-ci ou dont la priorité est revendiquée sur ceux-ci, les brevets d'invention ("*letters Patent*") ou leurs "*continuations-in-part*", ou les titres correspondants étrangers, qui peuvent être consentis pour eux ou sur eux, pour toute la durée entière pour laquelle les dits brevets d'invention ("*Letters Patent*") peuvent être consentis, et toutes les demandes, requêtes, déclarations sous serment et cessions ou tout autre document ou acte qui peut être requis aux fins de donner plein effet à la cession et au transfert auquel il est procédé par les présentes ou auquel les parties ont souhaité procéder.

De temps en temps, postérieurement à la date des présentes, à la demande de l'une ou l'autre des parties au présent contrat, et aux frais de la partie requérante, chacune des parties au présent contrat signera et transmettra à la partie requérante les documents et entreprendra toute autre action que la partie requérante pourra raisonnablement demander aux fins de parfaire les effets des transactions visées par le présent contrat.

Le Cédant déclare et garantit qu'à la date de la signature du présent contrat et de son enregistrement, il est titulaire de l'intégralité des droits sur les inventions et les Brevets délivrés sur lesdites inventions, telles qu'identifiés ci-avant, que les dites inventions et Brevets n'ont fait l'objet d'aucun gage et nantissement, et qu'il a tout pouvoir pour procéder à la présente cession.

Le présent contrat de cession a été rédigé en anglais et en français. En cas de contradiction entre les deux versions, la version française prévaudra.

Le Centre National de La Recherche Scientifique
Le Cédant

Par _____

Titre _____

Pour le Directeur Général
et par Délégation
Le Délégué aux Entreprises par intérim
Joseph BAIXERAS

Attachment A

TITLE & DOCKET NAME	COUNTRY	FILING DATE	INVENTORS	SERIAL NUMBER	PATENT NUMBER	ISSUE DATE
NOV/1000 Provisional β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S. CON	8/10/98 04/28/99	Gilles Josselin Jean-Louis Imbach	60/096,110 60/131,352		
NOV/1000 Normal β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	8/10/99	Gilles Gosselin Jean-Louis Imbach Martin L. Bryant	09/371,747	6,395,716	5-28-02
NOV/1000 CON β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/14/01	Gilles Gosselin Jean-Louis Imbach Martin L. Bryant	10/022,276		
NOV/1000 CIP β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/10/99	Gilles Gosselin Jean-Louis Imbach Martin L. Bryant	09/459,150		
NOV/1000 CIP CON β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/14/01	Gilles Gosselin Jean-Louis Imbach Martin L. Bryant	10/022,148		
NOV/1000 PCT β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	PCT	8/10/99	Gilles Gosselin Jean-Louis Imbach Martin Bryant	PCT/US99/18149	WO 00/09531	2/24/00
	Australia	8/10/99		54757/99		
	Brazil	8/10/99		9912896-9		
	Canada	8/10/99		2,340,156		
	China	8/10/99		99809553.2 CN1320128A		

TITLE & DOCKET NAME	COUNTRY	FILING DATE	INVENTORS	SERIAL NUMBER	PATENT NUMBER	ISSUE DATE
	Europe	8/10/99		99941027.7 1 104 436 A	1 104 436 A	
	Hong Kong	8/10/99		01104418.5 1034083		
	India	8/10/99		IN/PCT/2001/ 00194/DEL		
	India DIV I	8/10/99		IN/PCT/2001/ 00465/DEL		
	Japan	8/10/99		2000-564981		
	S. Korea	8/10/99		2001-7001758		
	Mexico	8/10/99		1001507		
	Russian Federation	8/10/99		2001106651		
	Singapore	8/10/99		200102730-9		
NOV 1005 3'-Prodrugs of 2'deoxy-β-L-Nucleosides	U.S. Prov.	6/15/00	Martin L. Bryant; Gilles Gosselin Jean-Louis Imbach	60/212,100		
	U.S.	6/15/01		09/883,033		
	PCT	6/15/01		US01/19147		
	Argentina	6/15/01		010102881		
	Bolivia	6/15/01		007456		
	Chile	6/15/01		1381-2001		
	Egypt	11/4/01		1168/2001		
	Malaysia	6/15/01		PI20012807		
	Pakistan	6/15/01		552/2001		
	Paraguay	6/15/01		N/A		
	Peru	6/15/01		584/2001		
	Philippines	6/15/01		2001-01499		
	Uruguay	6/15/01		26.779		
	Venezuela	6/15/01		1265-2001		
	Taiwan	6/15/01		90114380		
	Thailand	6/15/01		066273		

06171.105004

UNITED STATES
PATENT AND
TRADEMARK OFFICE

OCTOBER 28, 2002

PTAS

SHERRY M. KNOWLES, ESQ.
191 PEACHTREE STREET
ATLANTA, GA 30303-1763

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

102199601A

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RECORDATION DATE: 08/19/2002

REEL/FRAME: 013193/0841
NUMBER OF PAGES: 4

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
NOVIRIO PHARMACEUTICALS LIMITED

DOC DATE: 05/28/2002

ASSIGNEE:
IDENIX PHARMACEUTICALS INC.
125 CAMBRIDGE PARK DR.
CAMBRIDGE, MASSACHUSETTS 02140

SERIAL NUMBER: 60132126
PATENT NUMBER:

FILING DATE: 04/30/1999
ISSUE DATE:

SERIAL NUMBER: 60096110
PATENT NUMBER:

FILING DATE: 08/10/1998
ISSUE DATE:

SERIAL NUMBER: 60131352
PATENT NUMBER:

FILING DATE: 04/28/1999
ISSUE DATE:

SERIAL NUMBER: 10022276
PATENT NUMBER:

FILING DATE: 12/14/2001
ISSUE DATE:

SERIAL NUMBER: 09459150 PATENT NUMBER: 6444652	FILING DATE: 12/10/1999 ISSUE DATE: 09/03/2002
SERIAL NUMBER: 10022148 PATENT NUMBER:	FILING DATE: 12/14/2001 ISSUE DATE:
SERIAL NUMBER: 09744038 PATENT NUMBER:	FILING DATE: 05/01/2001 ISSUE DATE:
SERIAL NUMBER: 60207538 PATENT NUMBER:	FILING DATE: 05/26/2000 ISSUE DATE:
SERIAL NUMBER: 09867110 PATENT NUMBER:	FILING DATE: 05/29/2001 ISSUE DATE:
SERIAL NUMBER: 60212100 PATENT NUMBER:	FILING DATE: 06/15/2000 ISSUE DATE:
SERIAL NUMBER: 09883033 PATENT NUMBER:	FILING DATE: 06/15/2001 ISSUE DATE:
SERIAL NUMBER: 60207674 PATENT NUMBER:	FILING DATE: 05/26/2000 ISSUE DATE:
SERIAL NUMBER: 60283276 PATENT NUMBER:	FILING DATE: 04/11/2001 ISSUE DATE:
SERIAL NUMBER: 09863816 PATENT NUMBER:	FILING DATE: 05/23/2001 ISSUE DATE:
SERIAL NUMBER: 60206585 PATENT NUMBER:	FILING DATE: 05/23/2000 ISSUE DATE:
SERIAL NUMBER: 09864078 PATENT NUMBER:	FILING DATE: 05/23/2001 ISSUE DATE:
SERIAL NUMBER: 60283393 PATENT NUMBER:	FILING DATE: 04/11/2001 ISSUE DATE:
SERIAL NUMBER: 10122252 PATENT NUMBER:	FILING DATE: 04/11/2002 ISSUE DATE:
SERIAL NUMBER: 60249532 PATENT NUMBER:	FILING DATE: 11/17/2000 ISSUE DATE:
SERIAL NUMBER: 10001868 PATENT NUMBER:	FILING DATE: 11/19/2001 ISSUE DATE:
SERIAL NUMBER: 60326184 PATENT NUMBER:	FILING DATE: 09/28/2001 ISSUE DATE:
SERIAL NUMBER: 60326192 PATENT NUMBER:	FILING DATE: 09/28/2001 ISSUE DATE:

SERIAL NUMBER: 09371747
PATENT NUMBER: 6395716

FILING DATE: 08/10/1999
ISSUE DATE: 05/28/2002

PAULA MCCRAY, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

08-22-2002

102199601

FORM-PTO-1595 **TRANSMITTAL OF DOCUMENTATION**
1-31-92 **PATENTS ONLY** **Atty. Docket** 06171.105004

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): Novirio Pharmaceuticals Limited 08/19/02
Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):
Name: Idenix Pharmaceuticals Inc.
Foreign Address:
Domestic Address: 125 Cambridge Park Dr.
City: Cambridge State: MA ZIP: 02140
Additional name(s) & address(es) attached?
☐ Yes ☒ No

3. Nature of Conveyance:
☐ Assignment ☐ Merger
☐ Security Agreement ☒ Change of Name
Other
Execution Date: 5/28/02

4. Application number (s) or patent numbers(s):
If this document is being filed together with a new application, the execution date of the application is:
A. Patent Application No.(s) see attached B Patent Registration No. (s)
Additional numbers attached ? ☒ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Sherry M. Knowles, Esq.
191 Peachtree Street
Atlanta, Georgia 30303-1763
Telephone No.: 404- 572- 4600
Facsimile No.: 404 572-5100

6. Number of applications and patents involved: 23

7. Total fee (37 CFR 3.41): $ 920
☒ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number
11-0980
(Attach duplicate copy of this page if paying by deposit account):

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy of the original document.

Sally Sexton — Sally Sexton — August 13, 2002
Name of Person Signing — Signature — Date

Total number of pages comprising cover sheet: 3

08/21/2002 TDIAZ1 00000095 60132126
01 FC:581 920.00 OP

Schedule

TITLE & DOCKET NAME	COUNTRY	FILING DATE	SERIAL NUMBER	PATENT NUMBER	ISSUE DATE
IDX 1001: Provisional Use of 3'-Azido-2',3'-Dideoxyuridine	U.S.	04/30/99	60/132,126		
IDX 1000 Provisional β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S. CON	8/10/98 04/28/99	60/096,110 60/131,352		
IDX 1000 Normal β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	8/10/99	09/371,747	6,395,716	5/28/02
IDX 1000CON β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/14/01	10/022,276		
IDX/1000 CIP β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/10/99	09/459,150		
IDX 1000 CIPCON β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/14/01	10/022,148		
IDX 1003 Substituted 6-Benzyl-4-Oxopyrimidines, Process for Their Preparation and Pharmaceutical Compositions Containing Them	US	07/17/99	09/744,038		
IDX 1004 Methods for Treating Hepatitis Delta Virus Infection with β-L-2' Deoxy-Nucleosides	U.S. Prov.	5/29/00	60/207,538		
	U.S.	5/29/01	09/867,110		
IDX 1005 3'-Prodrugs of 2'deoxy-β-L-Nucleosides	U.S. Prov.	6/15/00	60/212,100		
	U.S.		09/883,033		
IDX1006 Methods and Compositions for Treating Flaviviruses and Pestiviruses	U.S. Prov.	5/26/00 4/11/01	60/207,674 60/283,276		
	U.S.	5/26/01	09/863,816		

TITLE & DOCKET NAME	COUNTRY	FILING DATE	SERIAL NUMBER	PATENT NUMBER	ISSUE DATE
IDX1007 Methods and Compositions for Treating Hepatitis C Virus	U.S. Prov.	05/23/00	60/206,585		
	U.S.	05/23/01	09/864,078		
IDX1008 Phenylindoles For The Treatment Of HIV	U.S. Prov.	4/11/01	60/283,393		
	U.S.	4/11/02	10/122,252		
IDX1009 Methods for Inhibiting the Transmission of HIV Using Topically Applied Substituted 6-Benzyl-4-Oxopyrimidines	U.S. Prov.	11/17/00	60/249,532		
	U.S.	11/19/01	10/001,868		
IDX1013 Methods and Compositions for Treating Hepatitis C Virus	U.S. Prov.	9/28/01	60/326,184		
IDX1014 Methods and Compositions for Treating Flaviviruses and Pestiviruses	U.S. Prov.	9/28/01	60/326,192		

CR-81404

REGISTRAR OF COMPANIES
EXEMPTED
CAYMAN ISLANDS

Certificate of Incorporation On Change Of Name

I DO HEREBY CERTIFY that

NOVIRIO PHARMACEUTICALS LIMITED

having by Special Resolution dated 28th of May 2002 changed its name, is now incorporated under the name of

Idenix Pharmaceuticals, Inc.

Given under my hand and Seal at George Town in the Island of Grand Cayman this Twenty-Eighth day of May Two Thousand Two

(SGD. D.H. DIXON)

An Authorised Officer,
Registry of Companies,
Cayman Islands, B.W.I.

CERTIFIED TRUE COPY

WALKERS
ATTORNEYS-at-LAW
WALKER HOUSE, GEORGE TOWN
GRAND CAYMAN, CAYMAN ISLANDS

DATE: 5/7/2002

CERTIFIED TO BE A TRUE AND CORRECT COPY

SIG. _____

DONNELL H. DIXON
Asst. Registrar of Companies

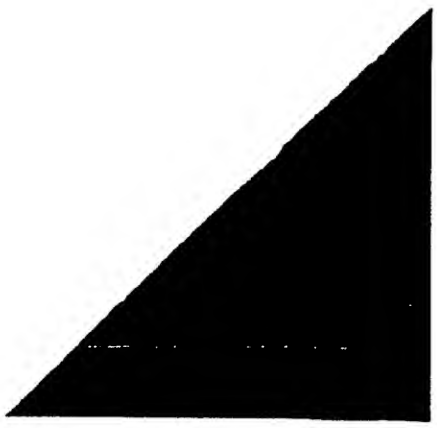
Date 28th May, 2002

CERTIFICATE OF MAILING (37 CFR § 1.8a)

I hereby certify that this Recordation of Assignment, along with any other paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Box Assignment, Assistant Commissioner for Patents, Washington, D.C. 20231.

Sally Sexton

06171.105004
Date: August 13, 2002



C.R

UNITED STATES
PATENT AND
TRADEMARK OFFICE

JUNE 11, 2003

PTAS

SHERRY M. KNOWLES, ESQ.
191 PEACHTREE STREET
ATLANTA, GA 30303-1763

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

102359457A

UNITED STATES PATENT AND TRADEMARK OFFICE
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RECORDATION DATE: 02/06/2003

REEL/FRAME: 013718/0543
NUMBER OF PAGES: 7

BRIEF: CERTICATE OF DOMESTICATION INCORPORATION IN DELAWARE

ASSIGNOR:
NOVIRIO PHARMACEUTICALS LIMITED

DOC DATE: 05/30/2002

ASSIGNEE:
IDENIX PHARMACEUTICALS INC.
125 CAMBRIDGE PARK DR.
CAMBRIDGE, MASSACHUSETTS 02140

SERIAL NUMBER: 60096110 — 105002
PATENT NUMBER:

FILING DATE: 08/10/1998
ISSUE DATE:

SERIAL NUMBER: 60131352 — 105002
PATENT NUMBER:

FILING DATE: 04/28/1999
ISSUE DATE:

SERIAL NUMBER: 10022276 — 105030
PATENT NUMBER: 6569837

FILING DATE: 12/14/2001
ISSUE DATE: 05/27/2003

SERIAL NUMBER: 10022148 IDX1000
PATENT NUMBER: 6566344

FILING DATE: 12/14/2001
ISSUE DATE: 05/20/2003

VDH Rec'd

JUN 17 2003

SERIAL NUMBER: 60207538 - 105011	FILING DATE: 05/26/2000
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09867110 - 105021	FILING DATE: 05/29/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60212100 - 105012	FILING DATE: 06/15/2000
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09883033 - 105026	FILING DATE: 06/15/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60207674 - 105008	FILING DATE: 05/26/2000
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60283276 - 105008	FILING DATE: 04/11/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09863816 - 105027	FILING DATE: 05/23/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60206585 - 105009	FILING DATE: 05/23/2000
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09864078 - 105022	FILING DATE: 05/23/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60283393 - 105013	FILING DATE: 04/11/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 10122252 - 105033	FILING DATE: 04/11/2002
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60249532 - 105014	FILING DATE: 11/17/2000
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 10001868 - 105030	FILING DATE: 11/19/2001
PATENT NUMBER: 6545007	ISSUE DATE: 04/08/2003
SERIAL NUMBER: 60326184 - 105018	FILING DATE: 09/28/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 60326192 - 105020	FILING DATE: 09/28/2001
PATENT NUMBER:	ISSUE DATE:
SERIAL NUMBER: 09371747 - 105005	FILING DATE: 08/10/1999
PATENT NUMBER: 6395716	ISSUE DATE: 05/28/2002
SERIAL NUMBER: 09459150 - 105007	FILING DATE: 12/10/1999
PATENT NUMBER: 6444652	ISSUE DATE: 09/03/2002

SAUNDRA BALLENGER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

02-07-2003

102359457

FORM-PTO-1595 **TRANSMITTAL OF DOCUMENT FOR RECORDATION** 2
1-31-92 **PATENTS ONLY** **Atty. Docket** 06171.105004

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): Novirio Pharmaceuticals Limited 2-6-03
Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):
Name: Idenix Pharmaceuticals Inc.
Foreign Address:
Domestic Address: 125 Cambridge Park Dr.
City: Cambridge State: MA ZIP: 02140
Additional name(s) & address(es) attached?
☐ Yes ☒ No

3. Nature of Conveyance:
☐ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☒ Other Certificate of Domestication; incorporation in Delaware
Execution Date: 5/30/02

4. Application number (s) or patent numbers(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s) B Patent Registration No. (s)

Additional numbers attached ? ☒ Yes ☐ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Sherry M. Knowles, Esq.
191 Peachtree Street
Atlanta, Georgia 30303-1763
Telephone No.: 404- 572- 4600
Facsimile No.: 404 572-5100

6. Number of applications and patents involved:
22

7. Total fee (37 CFR 3.41): $ 880
☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit account number
11-0980
(Attach duplicate copy of this page if paying by deposit account):

2003 FEB -6 AM 11:03
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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy of the original document.

Sally Sexton — Sally Sexton — January 30, 2003
Name of Person Signing — Signature — Date

Total number of pages comprising cover sheet: 3

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01 FC:8021 880.00 OP

Idenix Pharmaceuticals Patent Docket

TITLE & DOCKET NAME	COUNTRY	FILING DATE	SERIAL NUMBER	PATENT NUMBER	ISSUE DATE
IDX 1000 Provisional β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S. CON	8/10/98 04/28/99	60/096,110 60/131,352		
IDX 1000 Normal β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	8/10/99	09/371,747	6,395,716	5/28/02
IDX 1000CON β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/14/01	10/022,276		
IDX/1000 CIP β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/10/99	09/459,150	6,444,652	9/3/02
IDX 1000 CIPCON β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B	U.S.	12/14/01	10/022,148		
IDX 1004 Methods for Treating Hepatitis Delta Virus Infection with β-L-2' Deoxy-Nucleosides	U.S. Prov.	5/29/00	60/207,538		
	U.S.	5/29/01	09/867,110		
IDX 1005 3'-Prodrugs of 2'deoxy-β-L-Nucleosides	U.S. Prov.	6/15/00	60/212,100		
	U.S.		09/883,033		
IDX1006 Methods and Compositions for Treating Flaviviruses and Pestiviruses	U.S. Prov.	5/26/00 4/11/01	60/207,674 60/283,276		
	U.S.	5/26/01	09/863,816		
IDX1007 Methods and Compositions for Treating Hepatitis C Virus	U.S. Prov.	05/23/00	60/206,585		
	U.S.	05/23/01	09/864,078		
IDX1008 Phenylindoles For The Treatment Of HIV	U.S. Prov.	4/11/01	60/283,393		
	U.S.	4/11/02	10/122,252		

TITLE & DOCKET NAME	COUNTRY	FILING DATE	SERIAL NUMBER	PATENT NUMBER	ISSUE DATE
IDX1009 Methods for Inhibiting the Transmission of HIV Using Topically Applied Substituted 6-Benzyl-4-Oxopyrimidines	U.S. Prov.	11/17/00	60/249,532		
	U.S.	11/19/01	10/001,868		
IDX1013 Methods and Compositions for Treating Hepatitis C Virus	U.S. Prov.	9/28/01	60/326,184		
IDX1014 Methods and Compositions for Treating Flaviviruses and Pestiviruses	U.S. Prov.	9/28/01	60/326,192		

STATE OF DELAWARE
DIVISION OF CORPORATIONS
FILED 08:00 AM 05/30/2002
020342271 - 3530324

CERTIFICATE OF DOMESTICATION
OF
IDENIX PHARMACEUTICALS, INC.

It is hereby certified that:

1. Idenix Pharmaceuticals, Inc. (hereinafter called the "corporation") was first formed, incorporated, or otherwise came into being on May 1, 1998 in the jurisdiction of the Cayman Islands.

2. The name of the corporation immediately prior to the filing of this certificate of domestication pursuant to the provisions of Section 388 of the General Corporation Law of the State of Delaware is Idenix Pharmaceuticals, Inc.

3. The name of the corporation as set forth in its certificate of incorporation to be filed concomitantly with this certificate of domestication in accordance with subsection (b) of Section 388 of the General Corporation Law of the State of Delaware is Idenix Pharmaceuticals, Inc.

4. The jurisdiction that constituted the seat, siege social, or principal place of business or central administration of the corporation, or other equivalent thereto under applicable law immediately prior to the filing of this certificate of domestication pursuant to the provisions of Section 388 of the General Corporation Law of the State of Delaware is the jurisdiction of the Cayman Islands.

5. The undersigned is a corporation, officer, director, trustee, manager, partner, or other person performing functions equivalent to those of an officer or director, however named or described, and is authorized to sign this certificate of domestication on behalf of the corporation.

6. This certificate of domestication shall be effective at 9:00 a.m. on May 30, 2002.

Dated: May 30, 2002

/s/ Jean-Pierre Sommadossi
Jean Pierre-Sommadossi
Chief Executive Officer,
Idenix Pharmaceuticals, Inc.

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6. This certificate of domestication shall be effective at 9:00 a.m. on May 30, 2002.

Dated: May 30, 2002

Jean Pierre Sommadossi
Chief Executive Officer,
Idenix Pharmaceuticals, Inc.

Registrar of Companies,
Tower Building,
Grand Cayman.

Dear Sir,

IDENIX PHARMACEUTICALS, INC.

I, Andrea J. Corcoran, of 61 Garfield Street, Cambridge, MA 0218, being a director of Idenix Pharmaceuticals, Inc. (the "Company"), an exempted company incorporated under the Companies Law (2001 Second Revision), DO HEREBY make application, pursuant to Section 226 of the Companies Law (2001 Second Revision) for the Company to be deregistered in the Cayman Islands.

In support of this application:

1. I would advise that the Company has been accepted for domestication pursuant to Section 388 of the General Corporation Law of the State of Delaware, the United States of America. A copy of the Certificate of Domestication is attached to this application. I confirm that the laws of the State of Delaware, the United States of America permit the transfer of the Company to that jurisdiction and indeed that is the effect of the domestication procedure.

2. I enclose payment of US$2,414.63 (CI$1980) in respect of the fee for deregistration.

3. I confirm that the Company does not propose to change its name following deregistration.

4. I confirm that the Company has no secured creditors.

5. I confirm that the Company is not and has never been licensed under the provisions of the Banks and Trust Companies Law, (2001 Revision) or the Insurance Law, (2001 Revision).

I attach to this application

1. a certified copy of the Special Resolution of the Company adopted on ___ May 2002 resolving to register the Company by way of continuation in the State of Delaware, the United States of America;

2. a certified copy of the Resolution adopted by the Board of Directors of the Company dated May 6, 2002 resolving to apply for deregistration pursuant to Section 226 of the Companies Law (2001 Second Revision) and authorising me to make this application on behalf of the Company; and

3. my affidavit in support of this application in the terms prescribed by section 226(3) of the Companies Law (2001 Second Revision).

DATED this day of May 2002

Andrea J. Corcoran
Director
IDENIX PHARMACEUTICALS, INC.

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF DOMESTICATION OF "IDENIX PHARMACEUTICALS, INC.", FILED IN THIS OFFICE THE THIRTIETH DAY OF MAY, A.D. 2002, AT 8 O'CLOCK A.M.

AND I DO HEREBY FURTHER CERTIFY THAT THE EFFECTIVE DATE OF THE AFORESAID CERTIFICATE OF DOMESTICATION IS THE THIRTIETH DAY OF MAY, A.D. 2002, AT 9 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

3530324 8100D

020342271

AUTHENTICATION: 1802262

DATE: 05-30-02

Exhibit C

NDA 22-011

TYZEKA™
(telbivudine) Tablets

Rx only

Prescribing Information

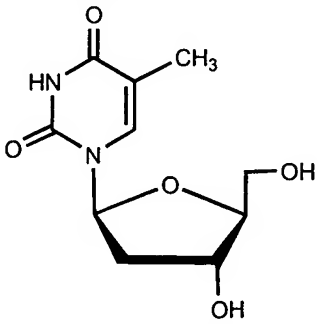
WARNINGS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including TYZEKA™ (telbivudine). Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted. (See WARNINGS.)

DESCRIPTION

TYZEKA™ is the trade name for telbivudine, a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). The chemical name for telbivudine is 1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione, or 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil. Telbivudine is the unmodified β-L enantiomer of the naturally occurring nucleoside, thymidine. Its molecular formula is $C_{10}H_{14}N_2O_5$, which corresponds to a molecular weight of 242.23. Telbivudine has the following structural formula:



Telbivudine is a white to slightly yellowish powder. Telbivudine is sparingly soluble in water (>20 mg/mL), and very slightly soluble in absolute ethanol (0.7 mg/mL) and n-octanol (0.1 mg/mL).

TYZEKA™ (telbivudine) film-coated tablets are available for oral administration in 600 mg strength. TYZEKA 600 mg film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet coating contains titanium dioxide, polyethylene glycol, talc and hypromellose.

MICROBIOLOGY

Mechanism of Action

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine 5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine 5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication. Telbivudine is an inhibitor of both HBV first strand (EC_{50} value = 1.3 ± 1.6 μM) and second strand synthesis (EC_{50} value = 0.2 ± 0.2 μM). Telbivudine 5'-triphosphate at concentrations up to 100 μM did not inhibit human cellular DNA polymerases α, β, or γ. No appreciable mitochondrial toxicity was observed in HepG2 cells treated with telbivudine at concentrations up to 10 μM.

Antiviral Activity

The antiviral activity of telbivudine was assessed in the HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus. The concentration of telbivudine that effectively inhibited 50% of viral DNA synthesis (EC_{50}) in both systems was approximately 0.2 μM. The anti-HBV activity of telbivudine was additive with adefovir in cell culture, and was not antagonized by the HIV NRTIs didanosine and stavudine. Telbivudine is not active against HIV-1 (EC_{50} value >100 μM) and was not antagonistic to the anti-HIV activity of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine.

Resistance

In an as-treated analysis of the Phase III global registration trial (007 GLOBE study), 59% (252/430) of treatment-naïve HBeAg-positive and 89% (202/227) of treatment-naïve HBeAg-negative patients receiving telbivudine 600 mg once daily achieved nondetectable serum HBV DNA levels (<300 copies/mL) by Week 52.

At Week 52, 145/430 (34%) and 19/227 (8%) of HBeAg-positive and HBeAg-negative telbivudine recipients, respectively, had evaluable HBV DNA (≥1,000 copies/mL). Genotypic analysis detected one or more amino acid substitutions associated with virologic failure (rtM204I, rtL80I/V, rtA181T, rtL180M, rtL229W/V) in 49 of 103 HBeAg-positive and 12 of 12 HBeAg-negative patients with amplifiable HBV DNA and ≥16 weeks of treatment. The rtM204I substitution was the most frequent mutation and was associated with virologic rebound (≥1 $\log_{10}$ increase above nadir) in 34 of 46 patients with this mutation.

Cross-Resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1,000-fold reduced susceptibility to telbivudine. Telbivudine retained wild-type phenotypic activity (1.2-fold reduction) against the lamivudine resistance-associated substitution rtM204V alone. The efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials. HBV encoding the adefovir resistance-associated substitution rtA181V showed 3- to 5- fold reduced susceptibility to telbivudine in cell culture. HBV encoding the adefovir resistance-associated substitution rtN236T remained susceptible to telbivudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

The single- and multiple-dose pharmacokinetics of telbivudine were evaluated in healthy subjects and in patients with chronic hepatitis B. Telbivudine pharmacokinetics are similar between both populations.

Absorption and Bioavailability

Following oral administration of telbivudine 600 mg once-daily in healthy subjects (n=12), steady state peak plasma concentration (C_{max}) was 3.69 ± 1.25 μg/mL (mean ± SD) which occurred between 1 and 4 hours (median 2 hours), AUC was 26.1 ± 7.2 μg·h/mL (mean ± SD), and trough plasma concentrations (C_{trough}) were approximately 0.2-0.3 μg/mL. Steady state was achieved after approximately 5 to 7 days of once-daily administration with ~1.5-fold accumulation, suggesting an effective half-life of ~15 hours.

Effects of Food on Oral Absorption

Telbivudine absorption and exposure were unaffected when a single 600-mg dose was administered with a high-fat (~55 g), high-calorie (~950 kcal) meal. TYZEKA™ (telbivudine) may be taken with or without food.

Distribution

In vitro binding of telbivudine to human plasma proteins is low (3.3%). After oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that telbivudine is widely distributed into tissues. Telbivudine was equally partitioned between plasma and blood cells.

Metabolism and Elimination

No metabolites of telbivudine were detected following administration of [^{14}C]-telbivudine in humans. Telbivudine is not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system (See CLINICAL PHARMACOLOGY. Drug Interactions.)

After reaching the peak concentration, plasma concentrations of telbivudine declined in a bi-exponential manner with a terminal elimination half-life ($T_{1/2}$) of 40 - 49 hours. Telbivudine is eliminated primarily by urinary excretion of unchanged drug. The renal

clearance of telbivudine approaches normal glomerular filtration rate suggesting that passive diffusion is the main mechanism of excretion. Approximately 42% of the dose is recovered in the urine over 7 days following a single 600 mg oral dose of telbivudine. Because renal excretion is the predominant route of elimination, patients with moderate to severe renal dysfunction and those undergoing hemodialysis require a dose interval adjustment (See DOSAGE AND ADMINISTRATION.)

Cardiac Safety

In an *in vitro* hERG model, telbivudine was negative at concentrations up to 10,000 μM. In a thorough QTc prolongation clinical study in healthy subjects, telbivudine had no effect on QT intervals or other electrocardiographic parameters after multiple daily doses up to 1800 mg.

Special Populations

Gender: There are no significant gender-related differences in telbivudine pharmacokinetics.

Race: There are no significant race-related differences in telbivudine pharmacokinetics.

Pediatrics and Geriatrics: Pharmacokinetic studies have not been conducted in children or elderly subjects.

Renal Impairment

Single-dose pharmacokinetics of telbivudine have been evaluated in patients (without chronic hepatitis B) with various degrees of renal impairment (as assessed by creatinine clearance). Based on the results shown in Table 1, adjustment of the dose interval for TYZEKA is recommended in patients with creatinine clearance of <50 mL/min (See DOSAGE AND ADMINISTRATION.)

Table 1. Pharmacokinetic Parameters (mean ± SD) of Telbivudine in Subjects with Various Degrees of Renal Function

	Renal Function (Creatinine Clearance in mL/min)				
	Normal (>80) (n=8) 600 mg	Mild (50-80) (n=8) 600 mg	Moderate (30-49) (n=8) 400 mg	Severe (<30) (n=6) 200 mg	ESRD/ Hemodialysis (n=6) 200 mg
C_{max} (μg/mL)	3.4±0.9	3.2±0.9	2.8±1.3	1.6±0.8	2.1±0.9
$AUC_{0\text{-}INF}$ (μg•hr/mL)	28.5±9.6	32.5±10.1	36.0±13.2	32.5±13.2	67.4±36.9
CL_{RENAL} (L/h)	7.6±2.9	5.0±1.2	2.6±1.2	0.7±0.4	

Renally Impaired Patients on Hemodialysis

Hemodialysis (up to 4 hours) reduces systemic telbivudine exposure by approximately 23%. Following dose interval adjustment for creatinine clearance (See DOSAGE AND

ADMINISTRATION), no additional dose modification is necessary during routine hemodialysis. TYZEKA should be administered after hemodialysis.

Hepatic Impairment

The pharmacokinetics of telbivudine following a single 600-mg dose have been studied in patients (without chronic hepatitis B) with various degrees of hepatic impairment. There were no changes in telbivudine pharmacokinetics in hepatically impaired subjects compared to unimpaired subjects. Results of these studies indicate that no dosage adjustment is necessary for patients with hepatic impairment.

Drug Interactions

Telbivudine is excreted mainly by passive diffusion so the potential for interactions between telbivudine and other drugs eliminated by renal excretion is low. However, because telbivudine is eliminated primarily by renal excretion, co-administration of telbivudine with drugs that alter renal function may alter plasma concentrations of telbivudine.

Drug-drug interaction studies show that lamivudine, adefovir dipivoxil, cyclosporine and pegylated interferon-alfa 2a do not alter telbivudine pharmacokinetics. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, or cyclosporine. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.

At concentrations up to 12 times that in humans, telbivudine did not inhibit *in vitro* metabolism mediated by any of the following human hepatic microsomal cytochrome P450 (CYP) isoenzymes known to be involved in human medicinal product metabolism: 1A2, 2C9, 2C19, 2D26, 2E1, and 3A4. Based on the above results and the known elimination pathway of telbivudine, the potential for CYP450-mediated interactions involving telbivudine with other medicinal products is low.

INDICATIONS AND USAGE

TYZEKA™ (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on virologic, serologic, biochemical and histologic responses after one year of treatment in nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease (See Description of Clinical Studies).

Description of Clinical Studies

Adults: The safety and efficacy of telbivudine were evaluated in an international active-controlled, clinical study of 1,367 patients with chronic hepatitis B, called the 007

GLOBE study. All subjects were 16 years of age or older, with chronic hepatitis B, evidence of HBV infection with viral replication (HBsAg-positive, HBeAg-positive or HBeAg-negative, HBV DNA detectable by a PCR assay), and elevated ALT levels ≥1.3 times the upper limit of normal (ULN), and chronic inflammation on liver biopsy compatible with chronic viral hepatitis.

The Week 52 results of the 007 GLOBE study are summarized below.

Clinical Experience in Patients with Compensated Liver Disease: The 007 GLOBE study is a Phase III, randomized, double-blind, multinational study of telbivudine 600 mg PO once daily compared to lamivudine 100 mg once daily for a treatment period of up to 104 weeks in 1,367 nucleoside-naïve chronic hepatitis B HBeAg-positive and HBeAg-negative patients. The primary data analysis was conducted after all subjects had reached Week 52.

HBeAg-positive Subjects: The mean age of subjects was 32 years, 74% were male, 82% were Asian, 12% were Caucasian, and 6% had previously received alfa-interferon therapy. At baseline, subjects had a mean Knodell Necroinflammatory Score ≥7; mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 9.51 $\log_{10}$ copies/mL; and mean serum ALT was 146 IU/L. Pre- and post-liver biopsy samples were adequate for 86% of subjects.

HBeAg-negative Subjects: The mean age of subjects was 43 years, 77% were male, 65% were Asian, 23% were Caucasian, and 11% had previously received alfa-interferon therapy. At baseline, subjects had a mean Knodell Necroinflammatory Score ≥7; mean serum HBV DNA as measured by Roche COBAS Amplicor® PCR assay was 7.66 $\log_{10}$ copies/mL; and mean serum ALT was 137 IU/L. Pre- and post-liver biopsy samples were adequate for 92% of patients.

Clinical Results (007 GLOBE Study)

Clinical and virologic efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative subject populations in Study 007.

Table 2. Histological Improvement and Change in Ishak Fibrosis Score at Week 52 (007 GLOBE Study)

	HBeAg-positive (n =797)		HBeAg-negative (n =417)	
	Telbivudine 600 mg (n=399)[1]	**Lamivudine 100 mg (n=398)[1]**	**Telbivudine 600 mg (n=205)[1]**	**Lamivudine 100 mg (n=212)[1]**
Histologic Response[2]				
Improvement	69%	60%	69%	68%
No Improvement	19%	26%	23%	25%
Missing Week 52 Biopsy	12%	15%	8%	7%
Ishak Fibrosis Score[3]				
Improvement	41%	46%	48%	44%
No Change	39%	32%	34%	43%
Worsening	9%	7%	10%	5%
Missing Week 52 Biopsy	12%	15%	8%	7%

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥ 2

[2] Histologic Response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score

[3] For Ishak Fibrosis Score, improvement defined as a ≥ 1-point reduction in Ishak fibrosis score from Baseline to Week 52

The primary endpoint of Therapeutic Response at Week 52 is a composite serologic endpoint requiring suppression of HBV DNA to < 5 $\log_{10}$ copies/mL in conjunction with either loss of serum HBeAg or ALT normalized. Secondary endpoints included Histologic Response, ALT normalization, and various measures of antiviral efficacy.

In HBeAg-positive patients, 75% of the telbivudine subjects and 67% of the lamivudine subjects had a Therapeutic Response. In HBeAg-negative patients, 75% of the telbivudine subjects and 77 % of the lamivudine subjects had a Therapeutic Response.

Selected virologic, biochemical, and serologic outcome measures are shown in Table 3.

Table 3. Virological, Biochemical and Serologic Endpoints at Week 52 (007 GLOBE Study)

Response Parameter	HBeAg-positive (n =921)		HBeAg-negative (n =446)	
	Telbivudine 600 mg (n=458)	Lamivudine 100 mg (n=463)	Telbivudine 600 mg (n=222)	Lamivudine 100 mg (n=224)
Mean HBV DNA Reduction from Baseline (log_{10} copies/mL) ± SEM[1,2]	-6.45 (0.11)	-5.54 (0.11)	-5.23 (0.13)	-4.40 (0.13)
% Subjects HBV DNA Negative by PCR	60%	40%	88%	71%
ALT Normalization[3]	77%	75%	74%	79%
HBeAg Seroconversion[4]	23%	22%	NA	NA
HBeAg Loss[4]	26%	23 %	NA	NA

1. Roche COBAS Amplicor® Assay (LLOQ≤300 copies/mL)
2. HBeAg-positive: n=443 and 444, HBeAg-negative: n=219 for both telbivudine and lamivudine groups, respectively. Difference in populations due to exclusion of observations after treatment discontinuation due to efficacy and initiation of nonstudy anti-HBV drugs
3. HBeAg-positive: n=440 and 446, HBeAg-negative: n=203 and 207, for telbivudine and lamivudine groups, respectively. ALT normalization assessed only in subjects with ALT > ULN at baseline.
4. n=432 and 442, for telbivudine and lamivudine groups, respectively. HBeAg seroconversion and loss assessed only in subjects with detectable HBeAg at baseline.

Patients who achieved non-detectable HBV DNA levels at 24 weeks were more likely to undergo e-antigen seroconversion, achieve undetectable levels of HBV DNA, normalize ALT, and minimize resistance at one year.

CONTRAINDICATIONS

Telbivudine tablets are contraindicated in patients with previously demonstrated hypersensitivity to any component of the product.

WARNINGS

Exacerbations of Hepatitis After Discontinuation of Treatment

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (See ADVERSE REACTIONS, Exacerbations of Hepatitis After Discontinuation of Treatment.)

Skeletal Muscle

Cases of myopathy have been reported with telbivudine use several weeks to months after starting therapy. Myopathy has also been reported with some other drugs in this class.

Uncomplicated myalgia has been reported in telbivudine-treated patients (See ADVERSE REACTIONS). Myopathy, defined as persistent unexplained muscle aches and/or muscle weakness in conjunction with increases in creatine kinase (CK) values, should be considered in any patient with diffuse myalgias, muscle tenderness or muscle weakness. Among patients with telbivudine-associated myopathy, there has not been a uniform pattern with regard to the degree or timing of CK elevations. In addition, the predisposing factors for the development of myopathy among telbivudine recipients are unknown. Patients should be advised to report promptly unexplained muscle aches, pain, tenderness or weakness. Telbivudine therapy should be interrupted if myopathy is suspected, and discontinued if myopathy is diagnosed. It is not known if the risk of myopathy during treatment with drugs in this class is increased with concurrent administration of other drugs associated with myopathy, including corticosteroids, chloroquine, hydroxychloroquine, certain HMGCoA reductase inhibitors, fibric acid derivatives, penicillamine, zidovudine, cyclosporine, erythromycin, niacin, and/or azole antifungals. Physicians considering concomitant treatment with these or other agents associated with myopathy should weigh carefully the potential benefits and risks and should monitor patients for any signs or symptoms of unexplained muscle pain, tenderness, or weakness, particularly during periods of upward dosage titration.

PRECAUTIONS

General

Renal Function

Telbivudine is eliminated primarily by renal excretion, therefore dose interval adjustment is recommended in patients with creatinine clearance < 50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In addition, co-administration of TYZEKA™ (telbivudine) with drugs that affect renal function may alter plasma concentrations of telbivudine and/or the co-administered drug (See DOSAGE AND ADMINISTRATION).

Patients Resistant to Antiviral Drugs for Hepatitis B

There are no adequate and well controlled studies for telbivudine treatment of patients with established lamivudine-resistant hepatitis B virus infection. In cell culture, telbivudine is not active against HBV encoding amino acid substitutions M204I or M204V/L180M. Telbivudine retains wild-type phenotypic activity against the lamivudine resistance-associated substitution rtM204V alone; however, the efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials.

There are no adequate and well controlled studies for telbivudine treatment of patients with established adefovir-resistant hepatitis B virus infection. HBV encoding the adefovir resistance-associated substitution rtN236T remains susceptible to telbivudine, while HBV encoding an A181V amino acid substitution showed 3- to 5-fold reduced susceptibility to telbivudine in cell culture.

Liver Transplant Recipients

The safety and efficacy of telbivudine in liver transplant recipients are unknown. The steady-state pharmacokinetics of telbivudine was not altered following multiple dose administration in combination with cyclosporine. If telbivudine treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function should be monitored both before and during treatment with TYZEKA (See CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Information for Patients

A patient package insert (PPI) for TYZEKA is available for patient information.

Patients should remain under the care of a physician while taking TYZEKA. They should discuss any new symptoms or concurrent medications with their physician.

Patients should be advised to report promptly unexplained muscle weakness, tenderness or pain.

Patients should be advised that TYZEKA is not a cure for hepatitis B, that the long-term treatment benefits of telbivudine are unknown at this time and in particular, that the relationship of initial treatment response to outcomes such as hepatocellular carcinoma and decompensated cirrhosis is unknown.

Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that they should discuss any change in regimen with their physician.

Patients should be advised that treatment with TYZEKA has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (See PRECAUTIONS, Labor and Delivery).

Drug Interactions

Telbivudine is excreted mainly by passive diffusion so the potential for interactions between telbivudine and other drugs eliminated by renal excretion is low. However, because telbivudine is eliminated primarily by renal excretion, co-administration of telbivudine with drugs that alter renal function may alter plasma concentrations of telbivudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Telbivudine has shown no carcinogenic potential. Long term oral carcinogenicity studies with telbivudine were negative in mice and rats at exposures up to 14 times those observed in humans at the therapeutic dose of 600 mg/day.

There was no evidence of genotoxicity based on *in vitro* or *in vivo* tests. Telbivudine was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains with or without metabolic activation. Telbivudine was not clastogenic in mammalian-cell gene mutation assays, including human lymphocyte cultures and an assay with Chinese hamster ovary cells with or without metabolic activation. Furthermore, telbivudine showed no effect in an *in vivo* micronucleus study in mice.

In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at systemic exposures approximately 14 times that achieved in humans at the therapeutic dose.

Pregnancy Category B

Telbivudine is not teratogenic and has shown no adverse effects in developing embryos and fetuses in preclinical studies. Studies in pregnant rats and rabbits showed that telbivudine crosses the placenta. Developmental toxicity studies revealed no evidence of harm to the fetus in rats and rabbits at doses up to 1000 mg/kg/day, providing exposure levels 6- and 37-times higher, respectively, than those observed with the 600 mg/day dose in humans.

There are no adequate and well-controlled studies of telbivudine in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, telbivudine should be used during pregnancy only if potential benefits outweigh the risks.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to telbivudine, healthcare providers are encouraged to register such patients in the AntiRetroviral Pregnancy Registry by calling 1-800-258-4263.

Labor and Delivery

There are no studies in pregnant women and no data on the effect of telbivudine on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV infection.

Nursing Mothers

Telbivudine is excreted in the milk of rats. It is not known whether telbivudine is excreted in human milk. Mothers should be instructed not to breastfeed if they are receiving TYZEKA.

Pediatric Use

Safety and effectiveness of telbivudine in pediatric patients have not been established.

Geriatric Use

Clinical studies of telbivudine did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger subjects. In general, caution should be exercised when prescribing TYZEKA to elderly patients, considering the greater frequency of decreased renal function due to concomitant disease or other drug therapy. Renal function should be monitored in elderly patients, and dosage adjustments should be made accordingly. (See PRECAUTIONS, Renal Function and DOSAGE AND ADMINISTRATION.)

Special Populations

Telbivudine has not been investigated in co-infected hepatitis B patients (e.g., patients co-infected with HIV, HCV or HDV).

ADVERSE REACTIONS

Approximately 760 subjects have been treated with telbivudine in clinical studies at a dose of 600 mg once daily. Assessment of adverse reactions is primarily based on the pivotal 007 GLOBE study in which 1,367 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=680 patients) or lamivudine (n=687 patients) for up to 104 weeks. Median duration of treatment in the 007 GLOBE study was 60 weeks for telbivudine- and lamivudine-treated patients. The safety profiles of telbivudine and lamivudine were generally comparable in this study.

Clinical Adverse Events

In clinical studies telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity and not attributed to telbivudine. In the 007 GLOBE study patient discontinuations for adverse events, clinical disease progression or lack of efficacy were 0.6% for telbivudine and 2.0% for lamivudine. Frequently occurring adverse events regardless of attributability to telbivudine were upper respiratory tract infection (14%), fatigue and malaise (12%), abdominal pain

(12%), nasopharyngitis (11%), headache (11%), blood CPK increased (9%), cough (7%), nausea and vomiting (7%), influenza and influenza-like symptoms (7%), post-procedural pain (7%), diarrhea and loose stools (7%), pharyngolaryngeal pain (5%), pyrexia (4%), arthralgia (4%), rash (4%), back pain (4%), dizziness (4%), myalgia (3%), insomnia (3%), and dyspepsia (3%).

Frequently occurring adverse events regardless of attributability to lamivudine were headache (14%), upper respiratory tract infection (13%), abdominal pain (13%), fatigue and malaise (11%), nasopharyngitis (10%), influenza and influenza-like symptoms (8%), blood CPK increased (7%), cough (6%), post-procedural pain (6%), nausea and vomiting (6%), dyspepsia (5%), diarrhea and loose stools (5%), dizziness (5%), pharyngolaryngeal pain (4%), rash (4%), hepatic/RUQ pain (4%), arthralgia (4%), back pain (4%), pyrexia (3%), rhinorrhea (3%), ALT increased (3%), and pruritus (3%).

Selected, treatment-emergent, clinical adverse events of moderate to severe intensity, without consideration of study drug causality, during the pivotal 007 GLOBE study clinical trial are presented in Table 4.

Table 4. Selected Treatment-Emergent Clinical Adverse Events[a] (Grade 2-4) of Moderate to Severe Intensity Reported in the 007 GLOBE Study

Body System/Adverse Event	Telbivudine 600 mg (n=680)	Lamivudine 100 mg (n=687)
All subjects with any Grade 2-4 AE	22%	22%
General		
Fatigue/Malaise [b]	1%	1%
Pyrexia	1%	< 1%
Musculoskeletal & Connective Tissue		
Arthralgia	< 1%	1.0%
Muscle-Related Symptoms [c]	2 %	2 %
Gastrointestinal		
Abdominal Pain [d]	< 1%	< 1 %
Diarrhea/Loose Stools [e]	< 1%	< 1 %
Gastritis	< 1 %	0
Respiratory, Thoracic, & Mediastinal		
Cough [f]	< 1%	< 1 %
Nervous System		
Headache [g]	1%	2%

[a] Includes adverse events categorized as possibly/reasonably or not possibly/reasonably related to the treatment regimen by the Investigator. Excludes upper respiratory infection, pharyngitis/nasopharyngitis, post-procedural pain, influenza and influenza-like symptoms and laboratory abnormalities that were considered adverse events. Also excludes adverse events with a frequency of less than 0.7% in the LdT arm.

[b] Includes preferred terms: fatigue and malaise

[c] Includes preferred terms: back pain, fibromyalgia, muscle cramp, musculoskeletal chest pain, myalgia, myopathy, pain, pain in extremity, and tenderness.

[d] Includes preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain. Adverse events under preferred term "abdominal pain upper" with an

event or lower level term descriptions of right upper quadrant pain were excluded from the abdominal pain category and coded under hepatic pain/RUQ pain.

e. Includes preferred terms: diarrhea, loose stools, and frequent bowel movements

f. Includes preferred terms: cough and productive cough

g. Includes preferred terms: headache, migraine, sinus headache, and tension headache

Frequencies of selected treatment-emergent laboratory abnormalities in the 007 GLOBE study are listed in Table 5.

Table 5. Selected Treatment-Emergent Grade 3-4 Laboratory Abnormalities[1] in Patients with Chronic Hepatitis B in the 007 GLOBE Study

Test	Telbivudine 600 mg (n=680)	Lamivudine 100 mg (n=687)
Creatine Kinase (CK) ≥ 7.0 x ULN	9%	3%
ALT > 10.0 x ULN and 2.0 x baseline[2]	3%	5%
ALT (SGPT) > 3.0 x baseline	4%	8%
AST (SGOT) >3.0 x baseline	3%	6%
Lipase >2.5 x ULN	2%	4 %
Amylase > 3.0 x ULN	< 1%	< 1%
Total Bilirubin > 5.0 x ULN	< 1%	< 1%
Neutropenia (ANC ≤ 749/mm^3)	2%	2%
Thrombocytopenia (Platelets ≤ 49,999/mm^3)	< 1%	< 1%

[1] On-treatment value worsened from baseline to Grade 3 or Grade 4 during therapy

[2] American Association for the Study of Liver Diseases (AASLD) definition of acute hepatitis flare

Creatine kinase (CK) elevations were more frequent among subjects on telbivudine treatment, as shown above in Table 5. CK elevations occurred in both treatment arms; however median CK levels were higher in telbivudine-treated patients by Week 52. Grade 1-4 CK elevations occurred in 72% of telbivudine-treated patients and 42% of lamivudine-treated patients, whereas Grade 3/4 CK elevations occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients. Most CK elevations were asymptomatic but the mean recovery time was longer for subjects on telbivudine than subjects on lamivudine. While there was not a uniform pattern with regard to the type of adverse event and timing with respect to the CK elevation, 8% of telbivudine-treated patients with Grade 1-4 CK elevations experienced a CK-related adverse event[1] (within a 30-day window) compared to 6% of lamivudine-treated patients. In this subgroup of patients with CK-related adverse events, 9% of telbivudine-treated patients subsequently interrupted or discontinued study drug. These patients recovered after study drug discontinuation or interruption. Less than 1 % of telbivudine-subjects overall (n=3/680) were diagnosed with myopathy with muscular weakness; these patients also recovered after study drug discontinuation (See WARNINGS, Skeletal Muscle).

[1] Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, and pain in extremity.

As shown in Table 5, on-treatment ALT elevations were more frequent on lamivudine treatment. Additionally, the overall incidence of on-treatment ALT flares, using AASLD criteria (ALT > 10 x ULN and > 2.0 x baseline), was slightly higher in the lamivudine arm (5.1%) than the telbivudine arm (3.2%). The incidence of ALT flares was similar in the two treatment arms in the first six months. ALT flares occurred less frequently in both arms after Week 24, with a lower incidence in the telbivudine arm (0.4%) compared to the lamivudine arm (2.2%). For both lamivudine and telbivudine subjects, the occurrence of ALT flares was more common in HBeAg positive subjects than in HBeAg negative subjects. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations of Hepatitis After Discontinuation of Treatment (See WARNINGS)

There are insufficient data on post-treatment exacerbations of hepatitis after discontinuation of telbivudine treatment.

DRUG ABUSE AND DEPENDENCE

Telbivudine is not a controlled substance and no potential for dependence has been observed.

OVERDOSAGE

There is no information on intentional overdose of telbivudine, but one subject experienced an unintentional and asymptomatic overdose. Healthy subjects who received telbivudine doses up to 1800 mg/day for 4 days had no increase in or unexpected adverse events. A maximum tolerated dose for telbivudine has not been determined. In the event of an overdose, telbivudine should be discontinued, the patient must be monitored for evidence of toxicity, and appropriate general supportive treatment applied as necessary.

In case of overdosage, hemodialysis may be considered. Within 2 hours, following a single 200-mg dose of telbivudine, a 4-hour hemodialysis session removed approximately 23% of the telbivudine dose.

DOSAGE AND ADMINISTRATION

Adults and Adolescents (≥16 years of age): The recommended dose of telbivudine for the treatment of chronic hepatitis B is 600 mg once daily, taken orally, with or without food. The optimal treatment duration has not been established.

Renally Impaired Subjects: Telbivudine may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment to the recommended dose of telbivudine is necessary in patients whose creatinine clearance is ≥50 mL/min. Adjustment of dose interval is required in patients with creatinine clearance <50 mL/min including those with ESRD on hemodialysis (Table 6). For patients with ESRD, telbivudine should be administered after hemodialysis.

Table 6. Dose Interval Adjustment of TYZEKA™ in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Dose of Telbivudine
≥ 50	600 mg once daily
30 – 49	600 mg once every 48 hours
< 30 (not requiring dialysis)	600 mg once every 72 hours
ESRD	600 mg once every 96 hours

No adjustment to the recommended dose of telbivudine is necessary in patients with hepatic impairment.

HOW SUPPLIED

TYZEKA™ (telbivudine) 600-mg tablets are white to slightly yellowish film-coated, ovaloid-shaped tablets, imprinted with "LDT" on one side.

Bottle of 30 tablets (NDC 24108-101-01) with child-resistant closure.

Storage

Store TYZEKA™ tablets in original container at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

For all medical inquiries call: 1-877-8-TYZEKA (1-877-889-9352).

Keep this and all drugs out of the reach of children.

TYZEKA™ is a registered trademark of Idenix Pharmaceuticals, Inc.

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Idenix PHARMACEUTICALS NOVARTIS

Manufactured by:

Novartis Pharma Stein AG
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Cambridge, MA 02139

Marketed by:

Idenix Pharmaceuticals, Incorporated
Cambridge, MA 02139

Novartis Pharmaceuticals Corporation

East Hanover, NJ 07936

Patient Information

Rx only

Tyzeka ™ (Tie-zee'-ka)

(generic name = **telbivudine**)

Tablets

Read this Patient Information that comes with Tyzeka before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about TYZEKA?

1. **Some people who have taken medicines like TYZEKA (a nucleoside analogue) have developed a serious condition called lactic acidosis** (buildup of an acid in the blood). Lactic acidosis is a medical emergency and must be treated in the hospital. **Call your healthcare provider right away if you get any of the following signs of lactic acidosis.**
    - You feel very weak or tired.
    - You have unusual (not normal) muscle pain.
    - You have trouble breathing.
    - You have stomach pain with nausea and vomiting.
    - You feel cold, especially in your arms and legs.
    - You feel dizzy or light-headed.
    - You have a fast or irregular heartbeat.
2. **Some people who have taken medicines like TYZEKA have developed serious liver problems called hepatotoxicity,** with liver enlargement (hepatomegaly) and fat in the liver (steatosis). **Call your healthcare provider right away if you get any of the following signs of liver problems.**
    - Your skin or the white part of your eyes turns yellow (jaundice).
    - Your urine turns dark.
    - Your bowel movements (stools) turn light in color.
    - You don't feel like eating food for several days or longer.
    - You feel sick to your stomach (nausea).
    - You have lower stomach pain.
3. **Some people who have taken medicines like TYZEKA have developed persistent unexplained muscle pain, muscle weakness or muscle tenderness.** If you develop any of these symptoms, call your healthcare provider right away.
4. **Your hepatitis B infection may get worse or become very serious if you stop taking TYZEKA.**
    - Take your TYZEKA exactly as prescribed.

- Be sure to refill your prescription or talk to your healthcare provider if you are running low on Tyzeka. Do not run out of TYZEKA.
- Do not stop taking your TYZEKA without talking to your healthcare provider.

Your health care provider will need to monitor your health and do regular blood tests to check your liver if you stop taking Tyzeka. Tell your healthcare provider right away about any new or unusual symptoms that you notice after you stop taking Tyzeka.

What is TYZEKA?

TYZEKA is a prescription medicine used for chronic infection with hepatitis B virus (HBV) in adults who also have active liver damage.

- TYZEKA will not cure HBV.
- TYZEKA may lower the amount of HBV in the body.
- TYZEKA may lower the ability of HBV to multiply and infect new liver cells.
- TYZEKA may improve the condition of your liver.

It is important to stay under your healthcare provider's care while taking TYZEKA. Your healthcare provider will test the level of the hepatitis B virus in your blood regularly.

Does TYZEKA lower the risk of passing HBV to others?

TYZEKA does not stop you from spreading HBV to others by sex, sharing needles, or being exposed to your blood. Talk with your healthcare provider about safe sexual practices that protect your partner. Never share needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades. A shot (vaccine) is available to protect people at risk from becoming infected with HBV.

Who should not take TYZEKA (telbivudine)?

Do not take TYZEKA if you are allergic to any of its ingredients. The active ingredient in TYZEKA is telbivudine. See the end of this leaflet for a complete list of ingredients in TYZEKA. Tell your healthcare provider if you think you have had an allergic reaction to any of these ingredients.

TYZEKA has not been studied in children and is not recommended for anyone less than 16 years old.

What should I tell my healthcare provider before I take TYZEKA?

Tell your healthcare provider about all of your medical conditions, including if you:

- **have kidney problems.** You may need a lower dose of TYZEKA.
- **are pregnant or planning to become pregnant.** It is not known if TYZEKA is safe to use during pregnancy. It is not known whether TYZEKA helps prevent a pregnant mother from passing HBV to her baby. You and your healthcare provider will need to decide if TYZEKA is right for you. If you use TYZEKA while you are pregnant, talk to your healthcare provider.
- **are breast-feeding.** It is not known if TYZEKA can pass into your breast milk or if it can harm your baby. Do not breast-feed if you are taking TYZEKA.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. TYZEKA may interact with other medicines that leave the body through the kidneys.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist.

How should I take TYZEKA?

- Take TYZEKA exactly as prescribed. Your healthcare provider will tell you how much TYZEKA to take. The usual dose of TYZEKA Tablets is one 600 mg tablet once daily by mouth. Your dose may be lower if you have kidney problems.
- To help you remember to take your TYZEKA, try to take it at the same time each day.
    - **Do not change your dose or stop taking TYZEKA without talking to your healthcare provider. Your hepatitis B symptoms may get worse or become very serious if you stop taking TYZEKA.** After you stop taking TYZEKA, it is important to stay under your healthcare provider's care. Your healthcare provider will need to do regular blood tests to check your liver.
    - **If you forget to take TYZEKA,** take it as soon as you remember and then take your next dose at its regular time. If it is almost time for your next dose, skip the missed dose. Do not take two doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do.
    - When your supply of TYZEKA starts to run low, get more from your healthcare provider or pharmacy. **Do not run out of TYZEKA.**
    - **If you take more than the prescribed dose of TYZEKA,** call your healthcare provider right away.

What are the possible side effects of TYZEKA?

TYZEKA may cause the following serious side effects (see **" What is the most important information I should know about TYZEKA? "**):

- **lactic acidosis and liver problems.**
- **unexplained muscle pain, weakness or tenderness**
- **a worse or very serious hepatitis if you stop taking it.**

The most common side effects of TYZEKA include tiredness, headache, fever, and muscle related symptoms. Less common side effects include stomach pain, joint pain, diarrhea, and cough. In some patients the results of some blood tests may worsen.

These are not all the side effects of TYZEKA. The list of side effects is **not** complete at this time because TYZEKA is still under study. Report any new or continuing symptom to your healthcare provider. If you have questions about side effects, ask your healthcare provider. Your healthcare provider may be able to help you manage these side effects.

How should I store TYZEKA?

- Store TYZEKA Tablets at room temperature, 59° to 86° F (15° to 30° C). They do not require refrigeration. Do not store TYZEKA Tablets in a damp place such as a bathroom medicine cabinet or near the kitchen sink.
- Keep the container tightly closed.
- Throw away TYZEKA when it is outdated or no longer needed by flushing tablets down the toilet.
- **Keep TYZEKA and all medicines out of the reach of children and pets.**

General information about TYZEKA: Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use TYZEKA for a condition for which it was not prescribed. Do not give TYZEKA to other people, even if they have the same symptoms you have. It may harm them. This leaflet summarizes the most important information about TYZEKA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TYZEKA that is written for healthcare professionals. You can also call 1-877-8-Tyzeka or visit the TYZEKA website at *www.TYZEKA.com.*

What are the ingredients in TYZEKA?

Active Ingredient: telbivudine

Inactive Ingredients in TYZEKA Tablets: microcrystalline cellulose, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, titanium dioxide, talc, macrogol, hypromellose.

Idenix Pharmaceuticals, Inc.

Cambridge, MA 02139 U.S.A.

Novartis Pharmaceuticals Corporation

East Hanover, NJ 07936 U.S.A.

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

Based on package insert dated October 2006

Issued October 2006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 22-011

Idenix Pharmaceuticals, Inc.
David H. Hallinan, PhD, Vice President, Regulatory Affairs
60 Hampshire Street
Cambridge, MA 02139

Dear Dr. Hallinan:

Please refer to your new drug application (NDA) dated December 30, 2005, received December 30, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyzeka™ (telbivudine) 600 mg film coated tablets.

We acknowledge receipt of your submissions dated February 13, 2006, February 21, 2006, February 22, 2006, March 3, 2006, March 23, 2006, March 27, 2006, April 18, 2006, April 28, 2006, May 2, 2006, May 11, 2006, May 18, 2006, May 31, 2006, June 7, 2006, July 12, 2006, August 18, 2006 August 28, 2006, September 14, 2006, September 15, 2006, September 25, 2006, September 28, 2006, October 4, 2006, October 12, 2006, October 16, 2006, October 18,2006, October 23, 2006, October 24, 2006 and October 25, 2006.

This new drug application provides for the use of Tyzeka™ (telbivudine) 600 mg film coated tablets for treatment of chronic hepatitis B (CHB) in patients with evidence of viral replication and active liver inflammation.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed labeling text and patient labeling.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert and patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-011**." Approval of this submission by FDA is not required before the labeling is used.

Submit content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We acknowledge your commitment to participate in the Antiretroviral Pregnancy Registry.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for birth to 16 years of age until such studies can be conducted. We will issue a formal pediatric written request to you.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study/substudy under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.

2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 years of age. Using doses selected based on the substudy listed under item 1 above, conduct a pediatric safety and efficacy study of telbivudine with efficacy based on virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**."

In addition, we note the following postmarketing study commitments, specified in your submission dated October 23, 2006. These commitments are listed below.

Clinical

1. Complete and submit the final study report for Study NV-02B-007, the 104-Week, Phase 3 registrational trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with HBeAg-positive and HBeAg-negative chronic hepatitis B and compensated liver disease.

Protocol submission: Study Ongoing
Final report submission: July 2007

2. Conduct and submit a final study report to evaluate the use of LdT in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (Blacks/African Americans, Hispanics).

   Protocol submission: June, 2007
   Final report submission: June 2010

3. Conduct and submit a final study report for an efficacy and safety study of telbivudine in subjects who are coinfected with HIV and HBV. This study should include analysis of virologic, biochemical, and serologic endpoints for both HIV and HBV. It should also include evaluation of safety, and evaluation of HBV and HIV resistance.

   Protocol submission: June, 2007
   Final report submission: June 2010

4. Complete and submit the final study report for Study NV-02B-011, the double-blind trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with chronic hepatitis B and decompensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: April 2010

5. Complete and submit the final study report for Study NV-02B-018, the open-label trial comparing the efficacy and safety of telbivudine to adefovir dipivoxil in subjects with HBeAg-positive compensated chronic hepatitis B.

   Protocol submission: Study Ongoing
   Final report submission: June 2007

6. Complete and submit the final study report for Study NV-02B-022, the open-label, non-comparative trial assessing the long-term antiviral efficacy and safety of telbivudine in subjects with HBeAg-positive and HBeAg-negative compensated and decompensated chronic hepatitis B that have been previously treated in Idenix-sponsored telbivudine studies.

   Protocol submission: Study Ongoing
   Final report submission: May 2012

Clinical Pharmacology

7. Conduct and submit a final study report for a study evaluating CYP induction potential for telbivudine using in vitro or in vivo studies.

   Protocol submission: January 2007
   Final report submission: January 2008

8. Conduct and submit a final study report(s) for in vitro studies to evaluate if telbivudine is a P-gp inhibitor.

   Protocol submission: January 2007
   Final report submission: January 2008

Microbiology

9. Conduct and submit a final study report for a study to determine the anti-HBV cell culture combination activity relationships of telbivudine with entecavir.

   Protocol submission: December 2006
   Final report submission: April 2007

10. Conduct and submit a final study report for a study to determine the anti-HBV combination activity relationships of telbivudine in cell culture with the HIV NRTIs abacavir, emtricitabine, lamivudine, tenofovir, zalcitibine, and zidovudine.

    Protocol submission: February 2007
    Final report submission: November 2007

11. Conduct and submit a final study report for a study to determine the susceptibility to telbivudine and adefovir of the HBV rtA181 variants, rtA181T and rtA181S.

    Protocol submission: Study Ongoing
    Final report submission: November 2007

12. Conduct and submit a final study report for a study to determine the susceptibility in cell culture of HBV harboring the following mutations of highly conserved amino acid residues among HBV isolates: R22C, W58G, L69P, L82M, P99L, L180M, L209V, T240I, I254F, P261L, G295E, A307V, L331F, or A342T. These amino acid substitutions were found in the viruses of patients who experienced virologic failure (serum HBV DNA levels ≥1,000 copies/mL at Week 52) to telbivudine therapy.

    Protocol submission: February 2007

Final report submission: February 2008 and December 2009

13. Conduct and submit a final study report for a study to determine the mitochondrial toxicity of telbivudine in growing muscle cells, cell lines and primary cells, and primary hepatocytes with appropriate controls to validate the results.

    Protocol submission: March 2007
    Final report submission: March 2008

14. Complete and submit a final study report for ongoing genotypic and phenotypic analyses of HBV DNA from patients who experience virologic failure to long-term telbivudine therapy (serum HBV DNA levels ≥1,000 copies/mL) in ongoing clinical trials.

    Protocol submission: Study Ongoing (NV-02B-007)
    Final report submission: July 2007 update for NV-02B-007 and then annually for those NV-02B-007 patients who roll-over to NV-02B-022 (July 2008 and July 2009).

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b) (2) (vii) and 314.81(b) (2) (viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at 301-796-0807.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D.
Acting Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure: approved draft labeling and patient package insert

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
10/25/2006 01:39:38 PM

Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Gosselin *et al.*

Serial No.: 10/022,276 Group Art Unit: 1623

Filed: December 14, 2001 Examiner: L. Eric Crane

For: β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B

Assistant Commissioner for Patents
Washington, DC 20231

July 17, 2002

Terminal Disclaimer

Sir:

Assignees, Novirio Pharmaceuticals Limited, Centre National de la Recherche Scientifique and the University of Montpellier II, the owners of entire interest of U.S. Serial Nos. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 and 10/022,148, through the undersigned agent of record, hereby disclaim the terminal part of any patent granted on U.S. Serial No. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 or 10/022,148 that would extend beyond the expiration date of the full statutory term of the other. Any patent granted on U.S. Serial No. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 or 10/022,148 shall be enforceable only for and during such period that legal title to one of the patents shall be the same as legal title to the other and will be binding upon the grantee, its successors or assigns.

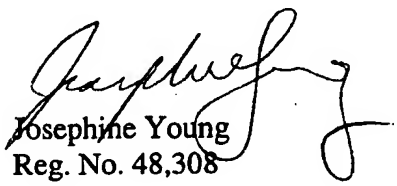
Gilles Gosselin has assigned U.S. Serial Nos. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 and 10/022,148 to the Centre National de la Reserche Scientifique, while Martin Bryant has assigned U.S. Serial Nos. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 and 10/022,148 to Novirio Pharmaceuticals Limited, whose addresses are of record, in an Assignment recorded on September 27, 1999, commencing at Reel 010271,

Frame 0725. Jean-Louis Imbach has assigned U.S. Serial Nos. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 and 10/022,148 to the Université Montpellier II, whose address was filed in an Assignment mailed on May 24, 2002.

Assignees do not disclaim any terminal part of any patent granted on U.S. Serial No. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 or 10/022,148 prior to the expiration date of the full statutory term to the other of U.S. Serial No. 10/022,276; 09/371,747, now U.S. Patent No. 6,395,716; 09/459,150 or 10/022,148 in the event that such patent later: a) expires for failure to pay a maintenance fee, b) is held unenforceable, c) is found invalid, d) is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. § 1.321(a), e) has all claims canceled by a reexamination certificate, or f) is otherwise terminated prior to expiration of its statutory term, except for the separation of legal title stated above.

Please charge the $110.00 fee for filing this Terminal Disclaimer, as well as any other fees required, to Deposit Account No. 11-0980.

Respectfully submitted,



Josephine Young
Reg. No. 48,308

KING & SPALDING
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Exhibit F

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WH 11/27/06

Exhibit 9

Table 1: List of Certain IND activities

Date	IND Serial No.	From	To	Description
11/22/2006	282	Idenix	FDA	New Protocol; NV-02B-029
11/22/2006		FDA	Idenix	Fax re review comments - Regarding the Oral Solution Briefing Book, SN 281
11/16/2006		FDA	Idenix	Fax re Microbiology Comments - Regarding Novartis Protocol CLDT600A2406 SN 275
11/2/2006	281	Idenix	FDA	Oral Solution Pre-NDA Briefing Book
11/1/2006	280	Idenix	FDA	Follow-up IND Safety Report NV-02B-011; AUV-382
10/25/2006	279	Idenix	FDA	15-day IND Safety Report NV-02B-022; AUV-380
10/25/2006	278	Idenix	FDA	7-day IND Safety Report NV-02B-011; AUV-382
10/25/2006		Idenix	FDA	Fax to Kenny Shade re 7-day IND Safety Report NV-02B-011; SN 278
10/20/2006	277	Idenix	FDA	Response to Agency's Clinical and Biometric Comments on SN 252; Amendment 2 for Protocol NV-02B-022
10/13/2006	276	Idenix	FDA	Request for Type B Meeting
10/11/2006		FDA	Idenix	Fax re Clinical and Microbiology Comments
10/6/2006	275	Idenix	FDA	New Protocol; CLDT600A2406
10/4/2006	274	Idenix	FDA	Follow-up IND Safety Report NV-02C-004; AUV-359
10/3/2006	273	Idenix	FDA	Follow-up IND Safety Report NV-02B-011; AUV-277
9/26/2006		FDA	Idenix	Fax re Biometric Comments
9/21/2006		Idenix	FDA	Fax to Beth Marchetto re generic name
9/15/2006	272	Idenix	FDA	Follow-up IND Safety Report NV-02B-007; AUV-121
9/13/2006	271	Idenix	FDA	Follow-up IND Safety Report NV-02C-004; AUV-359
9/13/2006		Idenix	FDA	Fax to Caroline Brann re AUV-359; NV-02C-004
8/30/2006	270	Idenix	FDA	IND Annual Report
8/29/2006	269	Idenix	FDA	Initial IND Safety Report; NV-02C-004; AUV-359; Nephrotic Syndrome
8/29/2006		Idenix	FDA	Fax to K. Shade re SN 269
8/16/2006	268	Idenix	FDA	Follow-up IND Safety Report NV-02B-022 AUV-293
8/15/2006	267	Idenix	FDA	New Phase IIIb Protocol NV-02B-027

Date	IND Serial No.	From	To	Description
8/11/2006	266	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-200
8/11/2006	265	Idenix	FDA	Initial IND Safety Report NV-02B-022 AUV-349
8/11/2006		Idenix	FDA	Fax to K. Shade re SN 265
8/8/2006	264	Idenix	FDA	4th Follow-up IND Safety Report NV-02B-007 AUV-121
8/8/2006		FDA	Idenix	Fax received re Biometrics comments re SN 252
8/4/2006	263	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-342 and SUV-303
8/4/2006	262	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-200
8/4/2006		Idenix	FDA	Fax to K. Shade re SN 262
8/3/2006		Idenix	FDA	Desk copy request sent to K. Shade re SN 252
7/26/2006	261	Idenix	FDA	Follow-up IND Safety Report NV-02B-022 AUV-293
7/20/2006	260	Idenix	FDA	Follow-up IND Safety report NV-02B-022 AUV-333
7/17/2006		FDA	Idenix	Fax received re Clinical Comments re SN252 NV-02B-022
7/12/2006	259	Idenix	FDA	IND Safety Report NV-02B-022 AUV-333 Death
7/12/2006		Idenix	FDA	Fax to K. Shade re SN 259 IND Safety Report AUV-333 - Death
6/30/2006	258	Idenix	FDA	Response to DAVP's June 22, 2006 Chemistry Comments regarding Serial 234 and 236
6/29/2006	257	Idenix	FDA	Response to Agency's Clinical Comments on SN 247 (fax dated June 23, 2006) Protocol NV-02B-028
6/23/2006	256	Idenix	FDA	Follow-up IND Safety Report AUV-303 NV-02B-011
6/23/2006		FDA	Idenix	Fax re Clinical Comments re SN 247
6/22/2006		FDA	Idenix	Fax re Comments on SN 234 and 236 re Oral Solution
6/21/2006	255	Idenix	FDA	Clinical Information Amendment: AUV-311
6/19/2006		Idenix	FDA	Fax to B. Breithaupt re audit of Prof. Liaw
6/16/2006	254	Idenix	FDA	Initial IND Safety Report AUV-303 NV-02B-011
6/16/2006		Idenix	FDA	Fax to K. Shade re SN 254

Date	IND Serial No.	From	To	Description
6/13/2006	253	Idenix	FDA	Follow-up IND Safety Report AUV-313 NV-02B-011
6/9/2006		Idenix	FDA	Email to K. Shade re fax sent June 8
6/8/2006		FDA	Idenix	Fax re Clinical Comments re SN 235 HIV/HBV
6/6/2006	252	Idenix	FDA	Protocol NV-02B-022; Amendment 2 and Addendum 1 (substudy) Version 1.0
6/5/2006	251	Idenix	FDA	7-day IND Safety Report NV-02B-011 AUV-313; Death from Septic Shock
6/5/2006		Idenix	FDA	Fax to K. Shade re SN 251
6/1/2006	250	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-306; Death from Upper Gastrointestinal Bleeding
5/26/2006	249	Idenix	FDA	Chemistry, Manufacturing and Controls CMC Amendment: changes to the Phase III /IV telbivudine (LDT) drug substance specifications
5/19/2006	248	Idenix	FDA	7-day IND Safety Report NV-02B-011 AUV-306 Death from Upper Gastrointestinal Bleeding
5/19/2006	247	Idenix	FDA	Response to Agency's Clinical Comments on SN 227 (fax dated April 4, 2006) Protocol NV-02B-028
5/19/2006		Idenix	FDA	Fax to K. Shade re SN 248
5/16/2006	246	Idenix	FDA	New Investigator Information for Protocol NV-02B-011
5/16/2006	245	Idenix	FDA	Revised Investigator Information for Protocol NV-02B-026
5/16/2006	244	Idenix	FDA	New and revised Investigator information for Protocol NV-02B-022
5/16/2006	243	Idenix	FDA	Revised Investigator Information for Protocol NV-02B-021
5/16/2006	242	Idenix	FDA	New and Revised Investigator Information for Protocol NV-02B-019
5/16/2006	241	Idenix	FDA	Revised Investigator Information for NV-02B-007
5/15/2006	240	Idenix	FDA	Response to Agency's April 20, 2006 Fax Clinical Comments on SN 232 (Protocol NV-02B-011)
5/12/2006	239	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-277; Death - Hepatorenal syndrome type 1

Date	IND Serial No.	From	To	Description
5/4/2006	238	Idenix	FDA	Initial 15-Day IND Safety Report NV-02B-022 AUV-293; Acute pancreatitis
5/4/2006		Idenix	FDA	Fax to K. Shade re SN 238 - IND Safety Report for NV-02B-022
5/3/2006	237	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-256; Severe Acsites
5/3/2006	236	Idenix	FDA	Chemistry, Manufacturing and Controls Pre-sNDA Briefing Book (CMC)
5/3/2006		FDA	Idenix	Email from K. Shade re received email regarding questions from Fax dated April 20, 2006 from Agency
5/1/2006	235	Idenix	FDA	Proposed Plan for HIV-HBV co-infected study
4/21/2006	234	Idenix	FDA	Request for Type B Meeting: Chemistry, Manufacturing and Controls (CMC)
4/20/2006		FDA	Idenix	Fax re Clinical Comments re safety reports and patient death summary and analysis for NV-02B-011 and going forward
4/12/2006	233	Idenix	FDA	Response to Agency's November 9, 2005 Chemistry Comments on SN 195 (Drug substance starting material: results of isomer testing on chlorosugar (CMC)
4/7/2006	232	Idenix	FDA	7-Day IND Safety Report NV-02B-011 AUV-277; Death from Hepatorenal syndrome type 1
4/7/2006	231	Idenix	FDA	Response to DAVDP's March 15, 2006 Clinical Comments on SN 218 Protocol NV-02B-026
4/7/2006		Idenix	FDA	Fax to K. Shade re 7-Day Safety Report NV-02B-011 SN 232
4/4/2006		FDA	Idenix	Fax re Clinical Comments re submission on March 21, 2006
3/27/2006	230	Idenix	FDA	Follow-up 7-Day IND Safety Report NV-02B-019 AUV-268; Death Suspected Cardiac Arrest
3/24/2006	229	Idenix	FDA	Response to DAVDP's Nov 14, 2005 Biometrics Comments and Nov 23, 2005 Clinical Comments on SN 191 (Protocol CLDT600A2404
3/22/2006	228	Idenix	FDA	Follow-up IND Safety Report NV-02B-011 AUV-265; Death from Multiple organ failure due to septic shock
3/21/2006	227	Idenix	FDA	New Protocol NV-02B-028

Date	IND Serial No.	From	To	Description
3/20/2006	226	Idenix	FDA	7-Day IND Safety Report NV-02B-019 AUV-268; Death - Unknown
3/16/2006	225	Idenix	FDA	Initial 15-day IND Safety Report for NV-02B-011; AUV-256; Severe Ascites
3/16/2006		FDA	Idenix	Fax from FDA re Clinical Comments to SN 218 submitted 2/7/06
3/15/2006	224	Idenix	FDA	Initial IND Safety Report for NV-02B-011; AUV-265; Death from Multiple Organ failure due to septic shock
3/15/2006	223	Idenix	FDA	Follow-up IND Safety Report for NV-02B-015; AUV-212; Death
3/15/2006		Idenix	FDA	Fax to K. Shade re Initial IND Safety Report for NV-02B-011; AUV-265; Serial 224
3/8/2006	222	Idenix	FDA	Follow-up IND Safety Report for NV-02B-015 AUV-217; Chronic Lymphandenitis
3/1/2006	221	Idenix	FDA	Protocol Amendment: Protocol NV-02B-026 (Amendment 1)
2/15/2006	220	Idenix	FDA	7-day IND Safety Report NV-02B-011 AUV-259 Event: Aspiration Pneumonia
2/9/2006	219	Idenix	FDA	7-Day IND Safety Report NV-02B-022; AUV-253; Event: Death Unknown
2/7/2006	218	Idenix	FDA	New Protocol (NV-02B-026); New Investigator; Chemistry, Manufacturing and Controls (CMC) Amendment
1/23/2006	217	Idenix	FDA	New and Revised Investigator Information for Protocol NV-02B-022
1/23/2006	216	Idenix	FDA	Revised Investigator Information for Protocol NV-02B-019
1/23/2006	215	Idenix	FDA	Revised Investigator Information for protocol NV-02B-018
1/23/2006	214	Idenix	FDA	Revised Investigator Information for protocol NV-02B-011
1/23/2006	213	Idenix	FDA	Revised Investigator Information for protocol NV-02B-007
12/22/2005	212	Idenix	FDA	Follow-up IND Safety Report NV-02B-015 AUV-212; Death
12/21/2005		FDA	Idenix	email from K. Shade re LdT Trade name tentative acceptance for SEBIVO
12/16/2005		Idenix	FDA	email to K. Shade re LDT Trade name - Sebivo
12/14/2005	211	Idenix	FDA	7-day follow-up IND Safety Report NV-02B-015 AUV-212; Death

Date	IND Serial No.	From	To	Description
12/14/2005	210	Idenix	FDA	Follow-up 15-day IND Safety Report NV-02B-015 AUV-217; Suspected Lymphoma
12/14/2005		Idenix	FDA	Fax to K. Shade re 7-day follow-up IND Safety Report NV-02B-015 AUV-212; Death
12/8/2005		FDA	Idenix	Clinical comments to SN 203 - pediatric deferral and waiver
12/2/2005	209	Idenix	FDA	Initial 15-day IND Safety Report NV-02B-015 AUV-217; Suspected Lymphoma
12/2/2005		Idenix	FDA	Fax to K. Shade re 15-day IND Safety Report NV-02B-015 - SN 209
11/23/2005		FDA	Idenix	Clinical comments on SN 191 - protocol CLDT600A2404
11/16/2005	208	Idenix	FDA	15-day Follow-up IND Safety Report NV-02B-010 AUV-85 Hepatitis B Flare
11/14/2005		FDA	Idenix	SN 191 - NVS P3b protocol (CLDT600A2404) biometrics comments
11/11/2005	207	Idenix	FDA	15-day follow-up IND Safety Report NV-02B-011 AUV-205; Death
11/9/2005		FDA	Idenix	Chemistry Comments regarding SN 195 - Chlorosugar starting material
11/8/2005	206	Idenix	FDA	CMC Amendment: Phase III Comparator (over-encapsulated lamivudine) Information
11/2/2005	205	Idenix	FDA	Initial Serious Adverse Event NV-02B-011; AUV-205; Death
11/2/2005		Idenix	FDA	Fax to J. O'Neill re SAE NV-02B-011; AUV-205
11/1/2005	204	Idenix	FDA	CMC Amendment for CLDT600A2404
10/28/2005	203	Idenix	FDA	Pediatric Deferral and Partial Waiver Request
10/28/2005	202	Idenix	FDA	3rd Follow-up Serious Adverse Event; NV-02B-007; AUV-121; Creatine Kinase Elevation
10/27/2005	201	Idenix	FDA	Follow-up Serious Adverse Event; NV-02B-007; AUV-156; Liver Failure
10/24/2005	200	Idenix	FDA	New Investigators for Protocol NV-02B-019
10/24/2005	199	Idenix	FDA	New and Revised Investigator Information re NV-02B-022
10/19/2005	198	Idenix	FDA	CMC Amendment: Packaging Update
10/17/2005	197	Idenix	FDA	7-Day IND Safety Report NV-02B-011 AUV-196 Event: Death

Date	IND Serial No.	From	To	Description
10/17/2005		FDA	Idenix	Email from Jeff O'Neill re FDA fax number
10/12/2005	196	Idenix	FDA	Follow-up 15-day IND Safety Report NV-02B-019; AUV-181; Event; Syncope; onset date 8/5/05
10/7/2005	195	Idenix	FDA	Pre-NDA Commitment: Drug Substance starting material: Results of isomer testing on chlorosugar: Chemistry, Manufacturing and Control (CMC)
10/6/2005	194	Idenix	FDA	2nd Follow-up 15-Day IND Safety Report; Protocol NV-02B-007; AUV-121; Event: creatine kinase elevation; Onset Date: 03/16/05
10/5/2005	193	Idenix	FDA	Pre-NDA commitment; 6-months Transgentic Mouse Carcinogenicity Report entitled: A 26-Week Oral Dose Carcinogenicity and Toxicokinetic Study of beta-L-2'-deoxythymidine in CB6F1-TgrasH2 Mice" (Study Number SNBL.046.11)
10/4/2005	192	Idenix	FDA	Pre-NDA Meeting follow-up: 1. Response regarding ISS/ISE request; 1. Synoptic clinical study report template
9/21/2005	191	Idenix	FDA	Protocol Amendment - New Protocol (Protocol CLDT600A2404) General Correspondence - Request for Division review - Novartis (NVS) Phase IIIb (P3b) protocol
9/20/2005	190	Idenix	FDA	Follow-up 15-Day IND Safety Report; Protocol NV-02B-019; AUV-181; Event: Syncope; Onset Date: 08/05/2005
9/14/2005	189	Idenix	FDA	Follow-up 15-day IND Safety Report NV-02B-007 AUV-156; Event: Liver Failure
9/13/2005		Idenix	FDA	Email to J. O'Neill re Sample eCTD submission
9/7/2005		FDA	Idenix	Email from Y. Murata re notification that he has left position as medical reviewer; new contact information
9/6/2005	188	Idenix	FDA	New Protocol NV-02B-021, Transfer of Obligations and New Investigator Information: Hu
8/30/2005	187	Idenix	FDA	IND Annual Report; Investigator's Brochure, Version 8.0

Date	IND Serial No.	From	To	Description
8/30/2005	186	Idenix	FDA	New Investigators for Protocol NV-02B-022: Heathcote, Lynch, Minuk, Myers, Shiffman, Wong
8/30/2005	185	Idenix	FDA	New Investigators for Protocol NV-02B-019: Berg, Diago, Guido, Piratvisuth, Tillman, Thongswat, Tran, Veitsman
8/30/2005	184	Idenix	FDA	Revised Investigators for Protocol NV-02B-011: Galati
8/25/2005	183	Idenix	FDA	Follow-up 15-day IND Safety Report Protocol NV-02B-007 AUV-156; Event: Liver Failure (fed-ex'd)
8/24/2005	182	Idenix	FDA	Initial 15-day IND Safety Report Protocol NV-02B-019 AUV-181 Event: Syncope (fed-ex'd and faxed to FDA)
8/23/2005		FDA	Idenix	Email re Change in Address for CDER beginning August 29, 2005
8/16/2005	181	Idenix	FDA	Chemistry, Manufacturing and Control (CMC) Amendment
8/12/2005	180	Idenix	FDA	Initial 15-day IND safety report Protocol NV-02B-007 AUV-156 Event: Liver Failure (also faxed to FDA)
8/12/2005	179	Idenix	FDA	Backup Proposed Proprietary Names: 1. Sebivo; 2. Tyzeka; 3. Tovanor
8/5/2005		FDA	Idenix	FAX - Statistical comments re SN 174 - SAP NV-02B-007
7/28/2005	178	Idenix	FDA	2-Year Rat Carcinogenicity Report (Volumes 1-8)
7/11/2005	177	Idenix	FDA	New and Revised Investigators' Information for Protocol NV-02B-007: Bassaris, Kurdas
7/11/2005	176	Idenix	FDA	New Investigators for Protocol NV-02B-019: Zuckerman
7/11/2005	175	Idenix	FDA	New Investigators for Protocol NV-02B-018: Cho, Han, Heathcote, Jeffers, Marcellin, Minuk, Tong
7/5/2005		Idenix	FDA	Email to Jeff O'Neill re NV-02B-007 Addendum to SAP - desk copy for Dr. Smith
7/1/2005	174	Idenix	FDA	Addendum to NV-02B-007 Statistical Analysis Plan (SAP)
6/23/2005		FDA	Idenix	Fax re Microbiology comments regarding SN 165

Date	IND Serial No.	From	To	Description
6/22/2005	173	Idenix	FDA	Response to DAVDP's March 14, 2005 Statistical Comments on SN 132 (Protocol NV-02B-024)
6/20/2005	172	Idenix	FDA	Response to DAVDP's June 2, 2005 Clinical Pharmacology Comment on SN 163 (Protocol NV-02B-022)
6/17/2005	171	Idenix	FDA	Handling and Submission of Data from Protocol NV-02B-011 in the NDA
6/16/2005	170	Idenix	FDA	New Investigators for Protocol NV-02B-019: Kitis, Papatheodoridis, Hilzenrat, Wong
6/15/2005		FDA	Idenix	Email from J. O'Neill re LdT Trade Name Appeal
6/14/2005	169	Idenix	FDA	Response to DAVDP's February 15, 2005 Statistical Comments on SN 125 Protocol NV-02B-019
6/14/2005	168	Idenix	FDA	Revised NV-02B-007 Statistical Analysis Plan (SAP) and Responses to DAVDP's June 6, 2005 Statistical Comments on SN 162 original SAP
6/14/2005	167	Idenix	FDA	New Investigators for Protocol NV-02B-022: Afdhal, Bennett, Bzowej, Chan, Chao, Dieterich, Han, Hann, Kwan, Lai, Lee, Liaw, Nguyen, O'Brien, Tong, Torres
6/14/2005		Idenix	FDA	Email from David Hallinan to Jeff O'Neill re LdT NV-02B-007 Revised SAP re June 6 faxed comments from Dr. Fraser Smith
6/13/2005	166	Idenix	FDA	Sample of Representative Dataset for Protocol NV-02B-007 Volumes 1-2
6/9/2005	165	Idenix	FDA	Sample Representative Dataset for Resistance Study
6/9/2005		Idenix	FDA	Email from David Hallinan to Jeff O'Neill re LdT Resistance Data Sample re desk copy for Dr. O'Rear
6/6/2005		FDA	Idenix	Fax from Jeff O'Neill - Statistical Comments regarding SN 162 - Protocol NV-02B-007
6/2/2005		FDA	Idenix	FAX - Clinical Pharmacology comments regarding SN 163
5/26/2005	164	Idenix	FDA	Follow-up 15-Day IND Safety Report Protocol NV-02B-015 AUV-133; Event: Acute Exacerbation of Chronic Hepatitis B

Date	IND Serial No.	From	To	Description
5/25/2005		Idenix	FDA	Email to Jeff O'Neill re Idenix Resistance Template Questions
5/24/2005	163	Idenix	FDA	Revised Protocol NV-02B-022; Amendment 1 and Responses to DAVDP's Clinical, Statistical and Microbiology comments (faxes dated January 13 and 27, 2005 and February 14, 2005
5/20/2005	162	Idenix	FDA	Proposed Statistical Analysis Plan (SAP) for Phase 3 Protocol NV-02B-007
5/16/2005	161	Idenix	FDA	New Investigators for Protocol NV-02B-019 Drs. Lake-Bakaar, George, Hann, Hou, Hwang, Lee, Lurie, Nimer, Wei, Weilert
5/16/2005	160	Idenix	FDA	New Investigators for Protocol NV-02B-018 Drs. Bzowej, Chao, Chutaputti, Crawford, Han, Heathcote, Minuk, Sievert, Tong
5/12/2005	159	Idenix	FDA	PowerPoint presentations and posters from DDW, EASL, and HepDART meetings
5/12/2005		FDA	Idenix	Pre-NDA meeting minutes April 5, 2005 re format and content of planned NDA for LdT
5/6/2005	158	Idenix	FDA	Revised Protocol NV-02B-024; Amendment 2; Response to DAVDP Clinical Comments (March 2, 2005 fax) QT/QTc
5/5/2005	157	Idenix	FDA	Protocol Amendment: Changes in Protocol NV-02B-025 (Amendment 1) - allowing subjects that smoke into study and to clarify study procedures.
5/4/2005	156	Idenix	FDA	Response to DAVDP's March 24, 2005 Chemistry Comments regarding Serial 133 and 135; pre-nda briefing book (CMC)
5/4/2005	155	Idenix	FDA	Initial 15-day IND Safety Report Protocol NV-02B-015 AUV-133 DOE: 4/20/05 DOR: 4/26/05 Event: Acute Exacerbation of Chronic Hepatitis B
5/4/2005	154	Idenix	FDA	Submission 154 VOID. Was originally planned for Protocol NV-02B-022 amendment 1 but this is now being held pending addnl possible revisions.

Date	IND Serial No.	From	To	Description
5/4/2005	153	Idenix	FDA	Follow-up IND Safety Report Protocol NV-02B-011 AUV-116 DOE: 1/26/05 DOR: 4/20/05
4/27/2005	152	Idenix	FDA	Appeal Regarding Proposed Proprietary Name APTIGARD re original proposal on Feb. 7, 2005 (SN 129)
4/26/2005	151	Idenix	FDA	Follow-up Safety Report Protocol NV-02B-007 AUV-28 DOE: 2/9/04 DOR: 4/25/05
4/21/2005	150	Idenix	FDA	New Investigator Info for Dr. W.C. Peter Kwan Protocol NV-02B-022
4/21/2005	149	Idenix	FDA	New Investigator Info for Drs. Chang, Ya-Gang, Jin, Kiong, Ngyuen, Safadi, Shiffman, Tong, Xie, Yin Protocol NV-02B-019
4/21/2005	148	Idenix	FDA	New Investigator Info for Drs. CHAN, Jeffers, Myers, Seng-Gee, Lai, Moon Protocol NV-02B-018
4/21/2005	147	Idenix	FDA	Revised Investigator Info for Dr. Leung and Dr. Tong Protocol NV-02B-010
4/20/2005	146	Idenix	FDA	15-day Follow-up Safety Report Protocol NV-02B-007 AUV-121; DOE: 3/16/05 DOR: 4/19/05
4/15/2005	145	Idenix	FDA	15-day Follow-up Safety Report Protocol NV-02B-010 AUV-85; DOE: 9/21/04 DOR: 4/14/05
4/14/2005	144	Idenix	FDA	New Protocol NV-02B-025; New Investigator Info - Dr. Marion; CMC Amendment
4/11/2005		FDA	Idenix	Comments re Submission serial number 136 and Pre-NDA meeting held April 5, 2005
4/1/2005		FDA	Idenix	Comments re submission serial number 136
3/31/2005	143	Idenix	FDA	Follow-up IND Safety Report Study: Phase III Protocol NV-02B-007 Manufacturer's Control No.: AUV-78 Event: Hyper Creatinine Kinase Date of Report: 3/31/05

Date	IND Serial No.	From	To	Description
3/31/2005	142	Idenix	FDA	Fed-ex to Debra Birnkrant 15-Day IND Safety Report from Phase III Protocol NV-02B-007 Manufacturer's Control No.: AUV-121 Event: Creatinine Kinase Elevation Date of Report: 3/31/05
3/31/2005		Idenix	FDA	Fax to Jeff O'Neill 15-day IND Safety Report Protocol NV-02B-007 Manufacturer's Control No.: AUV-121 Event: Creatinine Kinase Elevation Date of Report: 3/31/05
3/25/2005	141	Idenix	FDA	Response to DAVDP Microbiology Comments (October 4, 2004 fax) In vitro LdT Viral Resistance Pharmacology Reports
3/24/2005		FDA	Idenix	Chemistry comments re Submission serial numbers 133, 135
3/18/2005	140	Idenix	FDA	Follow-up IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-116 Event: Death "Unknown" Date of Report: 3/10/05
3/14/2005	139	Idenix	FDA	Follow-up IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-61 Event: Death due to "Subacute liver failure with multiorgan failure and sepsis" Date of Report: 3/1/05
3/14/2005		FDA	Idenix	Statistical comments re Submission number 132
3/10/2005	138	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-116 Event Outcome: Unknown - Death Date of Report: 3/9/05
3/9/2005	137	Idenix	FDA	Follow-up IND Safety Report Study: Phase III Protocol NV-02B-007 Manufacturer's Control No.: AUV-78 Event: Hyper Creatinine Kinase Date of Report: 3/8/05

Date	IND Serial No.	From	To	Description
3/8/2005		Idenix	FDA	Email from David Hallinan re discussion with Jeff O'Neill re FDA problem with Aptigard review
3/4/2005	136	Idenix	FDA	Desk Copies of Pre-NDA Meeting Briefing Book
3/3/2005	136	Idenix	FDA	Pre-NDA Meeting Briefing Book
3/2/2005	135	Idenix	FDA	Response to DAVDP's February 7, 2005 Chemistry, Manufacturing, Control (CMC) Comments Regarding Serial No. 126 Chlorosugar
3/2/2005		FDA	Idenix	Clinical comments re Submission serial number 132
2/25/2005		FDA	Idenix	Meeting Request Granted Letter for Pre-NDA meeting Type B scheduled on April 5, 2005
2/18/2005	133	Idenix	FDA	Chemistry, Manufacturing and Controls (CMC) Pre-NDA Briefing Book
2/15/2005		FDA	Idenix	Fax - Statistical comments re Submission serial number 125
2/14/2005	132	Idenix	FDA	Response to DAVDP's Clinical/Statistical Comments on SN 114 (QTc Prolongation Protocol Synopsis NV-02B-024) Full Protocol NV-02B-024
2/14/2005		FDA	Idenix	Fax - microbiology comments re submission serial number 111 Protocol NV-02B-022
2/11/2005		FDA	Idenix	Fax - Statistical comments re Submission serial number 110
2/9/2005	131	Idenix	FDA	Follow-up IND Safety Report Study: Phase III Protocol NV-02B-007 Manufacturer's Control No.: AUV-78 Event: Hyper Creatinine Kinase
2/9/2005		Idenix	FDA	Fax to K. Shade re SN 219
2/8/2005	130	Idenix	FDA	Fed-ex to Debra Birnkrant Case of GCP Non-compliance and Possible Scientific Misconduct in Protocol NV-02B-010; Copy of letter submitted to both FDA and OHRP

Date	IND Serial No.	From	To	Description
2/8/2005		Idenix	FDA	Fed-ex to David Lepay Case of GCP Non-compliance & Possible Scientific Misconduct in Protocol NV-02B-010
2/7/2005	129	Idenix	FDA	FedEx to Dr. Debra Birnkrant. Proposed Proprietary Name: APTIGARD
2/7/2005		FDA	Idenix	Fax - Chemistry, Manufacturing, Control (CMC) comments re Submission Serial Number 126 chlorosugar
2/2/2005		Idenix	FDA	Email from David Hallinan to Jeff O'Neill re LdT Pre-NDA Meeting Request
1/31/2005	128	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control Nos.: AUV-103; AUV-95 Event Outcome: Death Date of Report: January 26, 2005
1/28/2005	127	Idenix	FDA	Pre-NDA Type B Meeting Request
1/27/2005		FDA	Idenix	FDA Fax regarding Submission Serial Number 111; Statistical comments on Protocol NV-02B-022
1/21/2005	126	Idenix	FDA	Response to DAVDP's December 20, 2004 Chemistry Comments Regarding Serial No. 107 (CMC)
1/19/2005	125	Idenix	FDA	Response to DAVDP's November 24, 2004 Clinical and Statistical Comments on SN 105 (Protocol NV-02B-019)
1/17/2005	124	Idenix	FDA	Four 7-Day IND Safety Reports on one patient Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-82; AUV-84; AUV-93 and AUV-96; Taiwan Event outcome: Duodenal Ulcer; Hepatic Encephalopathy; Hepatic Encephalopathy; Peritonitis Bacterial (DEATH); Initial Report Date of Report: 12/03/2004; 12/14/2004; 01/10/2005; 01/12/2005

Date	IND Serial No.	From	To	Description
1/14/2005	123	Idenix	FDA	Response to DAVDP Clinical Comments on SN 112, 113, & 114 (FDA Faxes dated December 13, 14, 22, & 20, 2004)
1/14/2005		Idenix	FDA	E-mail from David Hallinan to Jeff O'Neil regarding LdT Pre-NDA Meeting Plans
1/13/2005		FDA	Idenix	FDA Fax regarding clinical comment on Submission Serial Number 111: Protocol NV-02B-022
1/10/2005		FDA	Idenix	FDA fax Clinical and statistical comment regarding submission 114: Draft QTc Protocol Synopsis: NV-02B-024
1/7/2005	122	Idenix	FDA	Response to DAVDP Clinical Comment (August 30, 2004 FDA fax dated). Regarding Protocol NV-02B-011, Amendment 1 submission.
1/5/2005	121	Idenix	FDA	New and Revised Investigator Information for protocol NV-02B-011. 11 investigators were submitted.
12/30/2004		FDA	Idenix	Certified Mail from the FDA regarding SN 112 & 113 and how Idenix 15-Day Safety Reports should be submitted to the FDA: SN 112: IND Safety Report on AUV-78; Event: Hyper Creatinine Kinase; Protocol NV-02B-007 SN 113: IND Safety Report on AUV-85; Event: Hepatitis B flare due to drug resistant mutants
12/23/2004	120	Idenix	FDA	FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007, second follow-up Report; Report dated 12/22/2004 Event: Possible drug-induced myopathy, Date of Event 02/09/2004; AUV-28
12/23/2004	119	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-015 Manufacturer's Control No.: AUV-83; China Event outcome: Death due to "murder". Initial Report Date of Report: 12/09/2004

Date	IND Serial No.	From	To	Description
12/23/2004	118	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-007 Manufacturer's Control No.: AUV-70; Korea Event outcome: Death due to "road traffic accident". Initial Report Date of Report: 11/10/2004
12/23/2004	117	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-68; Korea Event outcome: Death due to "hepatic encephalopathy". Followup report - initial report was never submitted. Date of Report: 11/29/2004
12/23/2004	116	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-17 (pre-randomization), United States Event outcome: Death due to "Portal Vein thrombosis". Initial report Date of Report: 01/27/2004
12/23/2004	115	Idenix	FDA	7-Day IND Safety Report Study: Phase III Protocol NV-02B-011 Manufacturer's Control No.: AUV-61, Singapore Event outcome: Death due to "hepatic encephalopathy". Followup report - initial report was never submitted. Date of Report: 11/08/2004
12/23/2004		Idenix	FDA	SN 114 - Email to Jeff O'Neill re Draft QT Protocol Synopsis

Date	IND Serial No.	From	To	Description
12/22/2004		FDA	Idenix	FDA Fax Clinical comments on submission Serial Numbers 112, 113, 114: SN 112: IND Safety Report on AUV-78; Event: Hyper Creatinine Kinase; Protocol NV-02B-007 SN 113: IND Safety Report on AUV-85; Event: Hepatitis B flare due to drug resistant mutants SN 114: Draft Protocol Synopsis: QTc Prolongation
12/20/2004		FDA	Idenix	FDA Fax Chemistry comments on submission Serial Number 107: chlorosugar starting material
12/17/2004	114	Idenix	FDA	Draft QTc Protocol Synopsis for Information Purposes to obtain DAVDP Feedback. Protocol NV-02B-024
12/16/2004	113	Idenix	FDA	FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-010, Initial Report; Report dated 12/14/2004 Event: Hepatitis B flare due to drug resistant mutants, Date of Event 09/21/2004; AUV-85
12/16/2004	112	Idenix	FDA	FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007, Initial Report; Report dated 12/15/2004; Event: hyper creatinine kinase, Date of Event 11/25/2004; AUV -78
12/13/2004		FDA	Idenix	FDA letter acknowledgement of receiving submission Serial Number 107: chlorosugar starting material
12/8/2004	111	Idenix	FDA	New Protocol NV-02B-022; New PI; Transfer of Obligation
12/8/2004	110	Idenix	FDA	response to FDA fax stats comments re: Protocol NV-02B-018 (fax dated Sept 17, 2004)

Date	IND Serial No.	From	To	Description
12/6/2004		FDA	Idenix	Fax clinical comments on SN 106-108: Protocol NV-02B-023 and Amendment I
12/2/2004	109	Idenix	FDA	Submission of LdT Abstracts presented at recent AASLD, ICAAC, and EASL mtgs key words: presentation
11/24/2004		FDA	Idenix	Fax Clinical & statistical comments on SN 105: Protocol NV-02B-019
11/22/2004	108	Idenix	FDA	Protocol NV-02B-023, Amendment I
11/11/2004	107	Idenix	FDA	Request for CMC Follow-up discussion from the EOP2 meeting: Chlorosugar
11/5/2004	106	Idenix	FDA	New Protocol NV-02B-023; Transfer of Obligation; New PI: Dr. Mark J. Allison
10/25/2004	105	Idenix	FDA	New Protocol NV-02B-019; Transfer of Obligation; New PI: Dr. Chow Wan Cheng
10/4/2004		FDA	Idenix	FAX - Stats comment regarding SN 097 - protocol NV-02B-018
9/23/2004	104	Idenix	FDA	New Investigator information for protocol NV-02B-015
9/23/2004	103	Idenix	FDA	New Investigator information for protocol NV-02B-011
9/23/2004	102	Idenix	FDA	Response to DAVDP Statistical comments (September 14, 2004 fax) Protocol NV-02B-011
9/17/2004		FDA	Idenix	FAX - Statistical/Clinical comments regarding SN 097 - protocol NV-02B-018
9/14/2004		FDA	Idenix	FAX - Response to David Hallinan's e-mail dated 9/13/04 requesting clarification of the FDA fax dated 09/13/04.
9/13/2004		FDA	Idenix	FAX - Clinical comments on SN 101; question on the Annual report regarding SAE submission.
8/30/2004	101	Idenix	FDA	IND Annual Report
8/26/2004	100	Idenix	FDA	New investigators for protocol NV-02B-010
8/26/2004	99	Idenix	FDA	New investigators for protocol NV-02B-011
8/20/2004	98	Idenix	FDA	CMC Amendment: Milling Facility site Change
8/20/2004	97	Idenix	FDA	New Protocol NV-02B-018 LdT vs. ADV; Transfer of Obligations; New PI Professor CL Lai.

Date	IND Serial No.	From	To	Description
8/16/2004	096	Idenix	FDA	New Protocol Amendment I to NV-02B-011 The primary purpose of this amendment is to change the inclusion and exclusion criteria and revise the statistics section to no longer include previously planned interim analyses.
7/19/2004	095	Idenix	FDA	New PIs for protocol NV-02B-011
7/16/2004	094	Idenix	FDA	Faxed to Jeff O'Neill and FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007, Follow-up Report; Report dated 07/05/04; Event: malaise and dizziness, Date of Event 04/28/04; AUV 30
7/1/2004	093	Idenix	FDA	New protocol NV-02B-016 China Phase I; Dr. Pei Hu CV/1572; and Transfer of Obligations
6/18/2004	092	Idenix	FDA	Response to FDA fax (fax dated 06/07/2004) regarding Submission Serial 075 Table 2, composition of the two LdT commercial formulation variants namely variant 005 and variant 006.
6/11/2004	091	Idenix	FDA	Amended 091: Record of FDA contact on 06-02-04 re: pediatric protocol proposal teleconference meeting with FDA
6/7/2004		FDA	Idenix	Fax: Chemistry comments regarding SN 075: FDA is requesting the quantitative composition of variant 006 because it was not in SN 075.
6/2/2004		Idenix	FDA	Telephone conference regarding the pediatric protocol proposal

Date	IND Serial No.	From	To	Description
5/11/2004	090	Idenix	FDA	Submitted as an IND: Response to DAVDP Request for Additional Safety Report - CPK data on a patient who was the subject of and IND Safety Report as well as from patients who experienced grade 3/4 elevations in the NV-02B-003 study, and information on all potentially related adverse events from LdT studies ongoing or completed.
5/10/2004	089	Idenix	FDA	Faxed to Jeff O'Neill and FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007, Initial Report; Report dated 05/04/04; Event: malaise and dizziness, Date of Event 04/28/04; AUV 30
4/30/2004	088	Idenix	FDA	New PI for protocol NV-02B-007
4/30/2004	087	Idenix	FDA	New PI for protocol NV-02B-011
4/30/2004	086	Idenix	FDA	New PI for protocol NV-02B-010
4/29/2004	085	Idenix	FDA	Amended 085: Record of FDA contact on 4/08/04 re: stats NV-02B-010 & NV-02B-011 teleconference meeting with FDA
4/26/2004		FDA	Idenix	Faxed regarding clinical comments to Serial Number 082; questions regarding protocol NV-02B-007 CPK measurement and requested to provide any related AEs including but not limited to myositis and muscle weakness).
4/23/2004	084	Idenix	FDA	Faxed to Jeff O'Neill and FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007, Follow-up Report; Report dated 04/08/04; Event: Rash, Date of Event 03/05/04
4/21/2004	083	Idenix	FDA	Proposed Plan for Pediatric Study

Date	IND Serial No.	From	To	Description
4/14/2004	082	Idenix	FDA	Faxed to Jeff O'Neill and FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007; Initial Report, Event: Myositis, PIN: 012/001; MCN: AUV-28, Onset Date:2/09/2004, Date of Report: 4/13/04
3/29/2004	081	Idenix	FDA	Response to FDA statistical comments (fax received on March 22, 2004) on Protocol NV-02B-010 Response to FDA clinical comments (fax received on February 23, 2004) on Protocol NV-02C-003
3/26/2004	080	Idenix	FDA	Faxed to Jeff O'Neill and FedEx to Dr. Debra Birnkrant. 15-Day IND Safety Report from the LdT (telbivudine) Protocol NV-02B-007, Initial Report; Report dated 03/24/04; Event: Rash, Date of Event 03/05/04
3/26/2004	079	Idenix	FDA	New Protocol NV-02B-015 (extension of NV-02B-007, Phase III, Chinese subjects) and Transfer of Obligation
3/22/2004		Idenix	FDA	E-mail: Regarding Decomp NV-02B-011 F/U Stats Para
3/19/2004	078	Idenix	FDA	Revised and New Investigator information for Protocol NV-02B-007. 9 New PIs, please see letter 5 Revised PIs' 1572, please see letter
3/19/2004	077	Idenix	FDA	New Investigator for Protocol NV-02B-011: Robert Brown, MD Joseph Galati, MD Paul Kwo, MD
3/16/2004	076	Idenix	FDA	Record of FDA Contact on February 27, 2004 regarding stats issue for protocol NV-02B-011

Date	IND Serial No.	From	To	Description
3/15/2004	075	Idenix	FDA	New Protocol: NV-02B-014; pilot BE study comparing CSF, to 2 variants of 600 mg and liquid formulation. New PI: James Kisicki, MD; CMC Amendment: liquid formulation, and 2 variants of 600 mg formulations
2/24/2004	074	Idenix	FDA	New Protocol Amendment 2 NV-02B-010
2/23/2004		FDA	Idenix	Fax from the FDA regarding Template for the presentation of HBV resistance date.
2/18/2004	073	Idenix	FDA	Submitted 26 principal investigators for protocol NV-02B-007. Please see the listing in the LdT correspondence binder. 2 Australia 2 Greece 1 Spain 6 China 2 Korea 1 Turkey 3 Czech Republic 3 Poland 3 UK 2 France 1 Singapore
2/13/2004	072	Idenix	FDA	poster presentation which will be presented at the Shanghai International Liver Congress, Feb 14-17,04 in Hong Kong, China (1-year data from Protocol No. NV-02B-003).
2/10/2004	071	Idenix	FDA	Revised Investigators' Information for protocol NV-02B-010: Drs. Lai and Leung
2/9/2004		Idenix	FDA	Faxed: Draft Response to the Statistical Comments received from DAVDP via fax on December 15, 2003
2/6/2004	070	Idenix	FDA	Response to FDA comments (fax received on November 26, 2003): Protocol NV-02B-012
2/4/2004	069	Idenix	FDA	Protocol Amendment (Study # NV-02C-003) and response to the FDA regarding FDA's fax on 01/08/04 clinical comment on Serial Number 065.

Date	IND Serial No.	From	To	Description
1/26/2004	068	Idenix	FDA	New PIs for protocol: NV-02B-007 Marc Deschenes Joseph Galati Steven-Huy Han Mandana Khalili Yun-Fan Liaw Kenneth O'Riordan Richard Pollard And FDA response to SN059 missing CV for Graeme MacDonald
1/20/2004	067	Idenix	FDA	CMC Amendment The amendment provides details of the transfer of LdT drug product and placebo Novartis/Patheon materials
1/20/2004	066	Idenix	FDA	Transfer of Obligation to: Quintiles, Novartis, Phase Forward New address Protocol NV-02B-011
12/19/2003	065	Idenix	FDA	New Protocol (LdT/monoval-LdC PK Interaction); New Investigator: C. Kisicki, M.D.; Protocol NV-02C-003
12/17/2003	064	Idenix	FDA	New Investigators for the 010 study; see 064 folder for all the names (8 total)
12/17/2003	063	Idenix	FDA	New Investigators for the 007 study; see 063 folder for all the names (2 total)
12/15/2003		FDA	Idenix	Clinical comments regarding IND 60,459, SN-062
12/10/2003		FDA	Idenix	Clinical comments regarding IND 60,459, SN-060
12/5/2003	062	Idenix	FDA	Response to Clinical and Statistical Comments regarding Protocol NV-02B-011 following a July 17, 2003 FDA conference call
12/5/2003		Idenix	FDA	Response to FDA Clinical & Statistical Comments on the LdT (telbivudine) Decompensated Protocol NV-02B-011 following a July 17, 2003 Conference Call.
11/26/2003		FDA	Idenix	Clinical comments regarding IND 60,459, SN-061

Date	IND Serial No.	From	To	Description
11/11/2003	061	Idenix	FDA	Submission of PEG-INF Interaction Study (Protocol NV-02B-012) + MDS CV/1572
11/7/2003	060	Idenix	FDA	Submission of Decomp. Protocol NV-02B-011 + Dr. Han CV/1572.
11/4/2003		FDA	Idenix	Clinical comments regarding submission serial number 059.
10/29/2003	059	Idenix	FDA	New Investigators for the 007 study; see 059 folder for all the names (41 total)
10/24/2003	058	Idenix	FDA	New Protocol NV-02B-013; New Investigator Dr. Alan Marion
9/11/2003		FDA	Idx	letter acknowledging request for chlorosugar meeting - set for Oct. 14th ; Type B meeting CMC Meeting
9/10/2003		Idenix	FDA	email re: LdT Rat Carco question
8/29/2003	057	Idenix	FDA	Annual Report; Investigator's Brochure Version 7
8/19/2003	056	Idenix	FDA	Request for CMC meeting (chlorosugar)
8/14/2003		FDA	Idenix	fax re: minutes from the Exec CAC meeting of 08/12/2003
8/12/2003		Idenix	FDA	response to FDA re: Exec CAC feedback
8/11/2003		FDA	Idenix	correspondence between DH and Jeff O'Neill regarding Exec CAC feedback -- original email sent 8/6/2003
7/23/2003	055	Idenix	FDA	New Investigators for Protocol NV-02B-007: Bernstein; Di Besceglie; Bouliere; Dietrich; Heathcote; Kwan; Lee; Lok; Minuk; Samuel; Thuluvath; Tong; Wong
7/23/2003	054	Idenix	FDA	New Invesitgators for Protocol NV-02B-010: Farley; Han; Kiong; Leung; Lai
7/22/2003	053	Idenix	FDA	Resubmission of Corrected Safety, Efficacy, & Renal/Hepatic PK Data; Protocols NV-02B-003; NV-02B-005, & NV-02B-006
7/21/2003	052	Idenix	FDA	Request for Assessment of Ongoing Rat Carcinogenicity Study
7/21/2003		FDA	Idenix	clinical comment regarding serial 048
7/17/2003		Idenix	FDA	teleconference to discuss LdT decompensated Protocol NV-02B-011
7/16/2003		FDA	Idenix	clinical comment regarding serial 051

Date	IND Serial No.	From	To	Description
7/10/2003		Idenix	FDA	Fax re: the corrected table 5 from the July 3rd LdT submission in preparation for the conference call with DAVDP on July 17th to discuss planned decompensated liver disease study.
7/3/2003	051	Idenix	FDA	Safety, Efficacy & Renal/Hepatic PK Data Update
7/2/2003	050	Idenix	FDA	Special Protocol Assessment; Carcinogenicity Protocol
6/30/2003	049	Idenix	FDA	LdT PK in Renal Dialysate
6/26/2003		FDA	Idenix	fax re: clinical comment regarding submission 048
6/13/2003	048	Idenix	FDA	NV-02B-011: Decompensated protocol for FDA feedback
6/13/2003		Idenix	FDA	email regarding DAVDP Clin Pharm request
5/21/2003	047	Idenix	FDA	submission of 18 Investigators for the 007 study
4/7/2003		Idenix	FDA	email regarding DAVDP Clin Pharm Request
1/17/2003	046	Idenix	FDA	Formal submission of above transgenic mouse study questions.
1/17/2003		FDA	Idx	fax of FDA response to Idenix transgenic mouse study questions
1/15/2003		Idenix	FDA	fax - follow-up questions re: LdT transgenic mouse carcinogenicity study
1/3/2003		FDA	Idenix	official meeting minutes from the EOP2 CMC meeting on 11/13/02 to discuss outstanding chemistry and manufacturing requirements prior to initiating Phase III program
12/16/2002		FDA	Idenix	C.call regarding transgenic mouse carcinogenicity protocol outline feedback
12/13/2002	045	Idenix	FDA	Submission of Revised NV-02B-007 Phase 3 Protocol
12/5/2002	044	Idenix	FDA	Submission of Polymorph Screen Report. CMC; EOP2 FDA request
12/3/2002	043	Idenix	FDA	Submission of new Phase IIb Extension Protocol NV-02B-010 (Amendment 1); plus FDA-1572 + CV for Dr. Robert Perillo.

Date	IND Serial No.	From	To	Description
11/26/2002		FDA	Idenix	Fax - clinical pharmacology comments regarding IND 60,459 submission serial numbers 040. Protocol NV-02B-006, Amendment 1& 2
11/18/2002	042	Idenix	FDA	Submission of ACTG HBV/HIV Protocol & Authorization for Crossreferencing IND.
11/14/2002		Idenix	FDA	fax to FDA re: minutes of conference call re: histology as primary endpoint
11/13/2002		Idenix	FDA	EOP2 CMC Meeting. See presentation.
11/12/2002		Idenix	FDA	re-fax to Jeff O'Neill the fax regarding additional data for FDA CMC meeting on November 13th
11/4/2002		Idenix	FDA	fax re: clarifications to the manufacturing process flow information originally included in the original CMC packet
10/30/2002		Idenix	FDA	conference call re: histology as the primary endpoint on Phase 3 protocol
10/29/2002		FDA	Idenix	Fax: Clinical comments re Amend 037 and 039 Histology as primary endpoint, etc.
10/25/2002		FDA	Idenix	Clinical Trials Data bank information
10/24/2002		FDA	Idenix	FDA called to postpone the Clin/Stats 10/23 conference call. They need to get additional opinions from others as it may be precedent setting. Will call next week to re-schedule.
10/23/2002		Idenix	FDA	conference call re: need for combination toxicology studies to support combination clinical trials
10/21/2002	041	Idenix	FDA	Minutes of Oct., 3, 2002 Carcinogenicity Conf. Call & Request Feedback on Outline Transgenic Mouse Study Design
10/18/2002		FDA	Idenix	Clinical Trials Data Bank notification.
10/17/2002	040	Idenix	FDA	Amendment 1 to Protocol NV-02B-005 (Hepatic PK) & Amendments 1, 2 to Protocol NV-02B-006 (Renal PK).
10/17/2002		Idenix	FDA	email - Combination tox studies
10/15/2002	039	Idenix	FDA	Request for FDA Conf. Call to discuss Stats Feedback.
10/10/2002	038	Idenix	FDA	Amendment 2 to Phase IIb Protocol (NV-02B-003)
10/3/2002		FDA	Idenix	FDA/Idenix conf. call to discuss carcinogenicity study plans.

Date	IND Serial No.	From	To	Description
10/2/2002		FDA	Idenix	Faxed list of FDA Statistical comments on Idenix statistical responses (submission 036).
9/30/2002	037	Idenix	FDA	Submission of Phase 3 Protocol (NV-02B-007).
9/20/2002		FDA	Idenix	Final EOP2 minutes
8/29/2002	036	Idenix	FDA	Resistance Report and Stats Responses (faxed 8/23-24/2002) submitted as official IND amendments.
8/29/2002	035	Idenix	FDA	2002 Annual Report
8/24/2002		Idenix	FDA	Faxed copy of Idenix Viral Resistance Report.
8/23/2002	034	Idenix	FDA	Submission of Amendment 1 to Protocol NV-02B-003 (Phase IIb).
8/23/2002		Idenix	FDA	Faxed copy of Idenix response to FDA's 7/15/02 Statistical comments re planned P3 protocol.
8/14/2002	033	Idenix	FDA	Submission of Renal PK protocol (NV-02B-006) + 3 PI 1572s+CVs
8/12/2002	032	Idenix	FDA	Submission of Hepatic PK protocol (NV-02B-005) + 3 PI 1572s+CVs
8/9/2002	031	Idenix	FDA	14C-ADME Protocol (NV-02B-009) + 1572/ PI CV
8/2/2002		FDA	Idenix	draft EOP2 minutes
7/15/2002		Idenix	FDA	Fax to FDA on food effect study: preliminary summary. AE data presented was monitored. Data have not been entered.
7/11/2002		FDA	Idenix	DRAFT minutes of meeting of the End of Phase II meeting on June 17, 2002
7/10/2002	030	Idenix	FDA	EOP2 CMC information package Covers Phase 3 manufacturing information
6/27/2002		Idenix	FDA	follow-up conference call to discuss outstanding statistical considerations which were not finalized at the June 17 EOP2 meeting
6/17/2002		Idenix	FDA	conference call re: EOP2/pre Phase 3 meeting to discuss the proposed LdT phase 3 study design
6/12/2002	029	Idenix	FDA	Submission of Brief Clinical Data Update prior to EOP2 meeting. NV-02B-003 Interim Analysis

Date	IND Serial No.	From	To	Description
5/31/2002	028	Idenix	FDA	Submission of CMC Amendment covering all PI/II CMC updates.
5/29/2002	027	Novirio	FDA	Notification of Sponsor name change.
5/28/2002	026	Novirio	FDA	Submission of Final Clinical Study Report (CSR) for Protocol NV-02B-002.
5/7/2002	025	Novirio	FDA	Submission of Food Effect Protocol (NV-02B-008) + PI
5/2/2002	024	Novirio	FDA	EOP2 Meeting Request+ Information Packet
4/17/2002	023	Novirio	FDA	Submission of Final Clinical & PK Reports for NV-02B-004
4/1/2002		FDA	Idenix	Microbiology comments
3/6/2002	022	Novirio	FDA	Submission of PI CVs+ 1572s (Drs. Farley; Rodriguez-Torres; Kim & Rubin).
3/5/2002	021	Novirio	FDA	Submission of final, audited 9-mo. monkey tox. Report.
3/4/2002		Novirio	FDA	Teleconference meeting with FDA & Novirio (+Sumitomo reps.) to discuss proposed Phase III study design.
3/1/2002		Idenix	FDA	additional information re: phase 3 design
2/27/2002		FDA	Idenix	clinical and clinical pharmacology comments for serial number 019
2/11/2002	020	Novirio	FDA	Submission of PI CVs+1572s (Poynard & Brunowicki).
2/8/2002		Novirio	FDA	c.call to discuss FDA feedback on phase II study design
1/24/2002	019	Novirio	FDA	Request for FDA Feedback on PIII Study Design
11/15/2001		Novirio	FDA	c.call to discuss Exec CAC Carcinogenicity protocol review faxed feedback
11/9/2001		FDA	Idenix	Minutes of Executive CAC meeting of 11/06/01
10/29/2001	018	Novirio	FDA	Submission of PI CVs+1572s (Tong; Lau; Lim; Teo; Lai; Leung)
10/29/2001		Novirio	FDA	c.call to discuss revised carc protocol(s)
10/24/2001		Idenix	FDA	conference call re: revised carcinogenicity protocol(s)
10/23/2001	017	Novirio	FDA	Submission of Revised Carcinogenicity Protocol.
10/18/2001		Idenix	FDA	Conference call to discuss design of the 13-week mouse TK study as a pre-cursor to the selection of the high dose for the mouse carcinogenicity study.

Date	IND Serial No.	From	To	Description
10/17/2001		Idenix	FDA	Follow-up to 10/10/01 conference call re: carcinogenicity protocol special assessment request
10/12/2001	016	Novirio	FDA	Submission of Amendment 2 to Protocol NV-02B-001
10/10/2001		Idenix	FDA	conference call regarding review of Novirio's proposed carcinogenicity protocols in rat & mouse
9/28/2001		Idenix	FDA	Follow-up to phone conversation with Dr. Gu regarding stability data in Ann. rept.
9/27/2001	015	Novirio	FDA	Submission of Special Assessment request for Carcinogenicity Protocol
9/19/2001		Novirio	FDA	c. call to discuss LdT IND Annual report, specifically pg. 38 (first para of stability section 2.2.1.2)
9/18/2001	014	Novirio	FDA	Submission of FDA-1572 Forms + CVs for Drs. Bloomer; Han; Hann; Lok; Perillo & Wong. Also copies of EASL poster, DDW abstract & poster, and Jan.01 Antimicrobial Agents & Chemotherapy article.
9/7/2001	013	Novirio	FDA	Submission of Response to FDA Request for Feedback re Hep.B Adv.Comm.Meeting.
8/31/2001		FDA	Idenix	Clinical comments to serial number 010
8/29/2001	012	Novirio	FDA	Submission of IND Annual Report, including revd. Inv.Brochure (Edition 5)
8/15/2001	011	Novirio	FDA	Submission of audited 6 month rat chronic toxicity report.
8/2/2001	010	Novirio	FDA	Submission of Phase IIB Protocol , 1st Investigator (Dr. D.Dieterich) 1572+CV, and Updated Inv. Brochure NV-02B-003
7/13/2001	009	Novirio	FDA	Submission of 800mg multiple dose healthy volunteer gender PK study (NV-02B-004).
7/13/2001		FDA	Novirio	Conf. call with FDA. They are very happy with the summary of tox. Studies performed & planned. The Pharm/Tox reviewer will need some time to review the 3 mo. audited rat & monkey reports prior to starting the PIIB study. The 6 mo. rat & 9 mo. monkey data can be submitted as the study is ongoing. No other concerns were raised re the Phase IIB protocol.

Date	IND Serial No.	From	To	Description
7/12/2001	008	Novirio	FDA	3 months rat & monkey audited interim tox. Reports, plus unaudited letter summary of Seg. I/II reproductive tox. Study in the rat. Summary of completed & planned tox. Studies faxed in preparation for 7/13 conf. call.
7/12/2001		Novirio	FDA	letter to FDA regarding the upcoming c. call to enclose the summary of tox studies completed, ongoing, and planned
7/11/2001		FDA	Novirio	Call from FDA requesting a conf. call on 7/13 to discuss adequacy of toxicity data to support PIIB study.
6/21/2001		FDA	Novirio	Faxed FDA comment on Submission 007 requesting PK evaluation is included.
5/25/2001	007	Novirio	FDA	Draft Phase IIb Protocol submitted for FDA review & comment
5/17/2001	006	Novirio	FDA	Amendment 1 to NV-02B-001 for 400 mg dose cohort.
5/2/2001		FDA	Novirio	FDA called to reply to Meeting Info. Packet. They will fax answers to P2 and gen. questions but unable to answer P3 questions. Schedule a conf call after Nov. review of answers.
4/25/2001	005	Novirio	FDA	Submission of FDA Meeting Information Packet (also filed to val-LdC IND)
4/13/2001	004	Novirio	FDA	Submission of LdT+LAM PK Interaction Study (Protocol NV-02B-002 at MDS)
3/23/2001		Idenix	FDA	call to request conference call to discuss LdT and val-L-dC clinical programs
3/12/2001	003	Novirio	FDA	Request for meeting with DAVDP (also filed to val-L-dC IND)
11/14/2000	002	Novirio	FDA	Updated Integrated Tox. Summary
9/5/2000		FDA	Novirio	Faxed comments to protocol NV-02B-001 (Microbiology, pertaining to COBAS)
8/15/2000		FDA	Novirio	Letter from FDA stating that 30-day review is complete and that the proposed study may proceed
8/9/2000	001	Novirio	FDA	Response to request for information (comments from 7/6 and 7/14)
7/14/2000		FDA	Novirio	Faxed comments to protocol NV-02B-001 (Pharm/Tox)
7/6/2000		FDA	Novirio	Faxed comments to protocol NV-02B-001 (except Pharm/Tox)

Date	IND Serial No.	From	To	Description
6/27/2000		Novirio	FDA	Follow up to request for information via phone
6/19/2000		Novirio	FDA	Follow up to request for information via phone including additional study reports requested by the Agency
6/9/2000		FDA	Novirio	Acknowledgement of receipt of IND 60,459
5/31/2000	000	Novirio	FDA	IND Original Submission Protocol NV-02B-001
2/28/2000		FDA	Idenix	Pre-IND comments
12/9/1999		Idenix	FDA	Pre-IND package

Table 2: List of Certain NDA Activities

Date	Correspondence	Description
16-Nov-2006	NDA Seq# 0028	FDA Form 3542
13-Nov-2006	NDA Seq# 0027	Final Printed Labeling
8-Nov-2006	Drug Product Listing	Final Printed Label for Tyzeka
1-Nov-2006	NDA Seq# 0026	Structured Product Labeling
27-Oct-2006	Fax	Approval Letter correction
26-Oct-2006	Drug Product Listing	FDA Form 2657 for Tyzeka
25-Oct-2006	Mail	Approval Letter for Tyzeka
25-Oct-2006	NDA Seq# 0025	Patient Package Insert
24-Oct-2006	NDA Seq# 0024	Acceptance of Post Marketing Commitments
23-Oct-2006	NDA Seq# 0023	Acceptance of Post Marketing Commitments
20-Oct-2006	Email	The label
18-Oct-2006	Email	FDA response to sponsors comments on PMC 101606
18-Oct-2006	NDA Seq# 0022	Responses to Agency Comments
17-Oct-2006	Email	Submissions update
13-Oct-2006	Email	Chemistry request for contain label
12-Oct-2006	Email	Idenix Resistance Proposal 12 Oct 2006 with micro modifications
12-Oct-2006	FDA Teleconference	Teleconference to review revised label and post-marketing commitments
12-Oct-2006	NDA Seq# 0021	Responses to Agency comments
11-Oct-2006	Email	Question on additional SAE of Nephrotic syndrome
6-Oct-2006	Email	micro response final oct 6 2006 idix-06-139 pdf
5-Oct-2006	FAX	Reviewer Comments - Chemistry Comments
4-Oct-2006	NDA Seq# 0020	Responses to Agency Comments
4-Oct-2006	Email	Microbiology list discussed in teleconference today
4-Oct-2006	FDA Teleconference	Teleconference to review Idenix and FDA Label Revisions
3-Oct-2006	Email	Discontinuation rate summary Oct 3 2006
2-Oct-2006	Email	Patient Package Insert
29-Sep-2006	Email	Additional analyses on CK and cell doubling times
28-Sep-2006	NDA Seq# 0019	Clinical Pharmacology Comments dated September 15, 2006
26-Sep-2006	Email	Tyzeka label revisions

25-Sep-2006	Email	More Information - re clarifications related to teleconference
22-Sep-2006	Email	Voicemail re stats
20-Sep-2006	FDA Teleconference	Teleconference to review FDA revised label
20-Sep-2006	Email	Carcinogenicity Datasets
19-Sep-2006	Email	Tyzeka Label - Word version of label
15-Sep-2006	FAX	Review comments re Clinical Pharmacology
14-Sep-2006	NDA Seq# 0018	Response to Clinical Comments: August 30, 2006 (email and teleconference); Response to Clinical Comments: September 11, 2006 (fax)
13-Sep-2006	Email	Sequence 0018
12-Sep-2006	Email	Responses to Fax rec'd Sept 11 2006
11-Sep-2006	Fax	Clinical comments re Table 14.1.3.3 results
1-Sep-2006	Email	Response to FDA Emailed questions from August 30, 2006
1-Sep-2006	NDA Seq# 0017	Transcription of Email Correspondences
30-Aug-2006	FDA Teleconference	Record of Contact for FDA Teleconference re clinical questions sent to Idenix on August 30, 2006
22-Aug-2006	Email	Sequence 0016
21-Aug-2006	NDA Seq# 0016	Minimum and Maximum Lab Values By Patient Dataset III; Clarification of STRATE Variable
17-Aug-2006	Email	Clarification re datasets LABBYPT and LABBYPT2
16-Aug-2006	Email	Email from K. Shade re laboratory abnormalities in dataset
1-Aug-2006	Email	Email from K. Shade re NDA questions/comments for Idx
14-Jul-2006	Email	Sequence 0015
12-Jul-2006	NDA Seq# 0015	Report NV-02B-007 - Addendum 2; Report NV-02B-016 - Correction to analysis datasets; Submission of Resistance Report IDIX-06-112 to NV-02B-RES1
7-Jun-2006	NDA Seq# 0014	Clinical Pharmacology Study D3501007
31-May-2006	NDA Seq# 0013	Minimum and Maximum Lab Values By Patient Dataset
24-May-2006	NDA Record of Contact	Record of Contact w/FDA re feedback regarding Labs dataset submitted in Sequence 0011

22-May-2006	Email	Email from K. Shade re submitting SAS datasets and full study report as outlined in Option 1
19-May-2006	Email	Email from K. Shade re Japan Phase I single dose study report D35001007
18-May-2006	NDA Seq# 0012	Individual Patient Profiles
11-May-2006	NDA Seq# 0011	Response to Clinical Comments dated April 24, 2006; Response to Clinical Comments dated April 21, 2006
9-May-2006	Email	Email re notification of sending of sequence 0011
5-May-2006	Email	Clarification email from K. Shade re SN 0008
3-May-2006	Email	Clarification to question 2 in April 20 fax from Agency
2-May-2006	NDA Seq# 0010	120-day Safety Update
28-Apr-2006	NDA Seq# 0009	Micro datasets requested by FDA
21-Apr-2006	Email	Email from K. Shade re single analysis dataset for all laboratory parameters for each subject
18-Apr-2006	NDA Seq# 0008	Response to Clinical Comments dated March 31, 2006
13-Apr-2006	Email	Question to K. Shade re Patient Information Leaflet
12-Apr-2006	Fedex	Requested Pre-Inspection Materials for Selected NV-02B-007 sites
31-Mar-2006	Fax	Clinical Comments re SN 0005 - response to clinical comments dated February 6, 2006
30-Mar-2006	Email	Notification of NDA submissions to Kenny Shade
27-Mar-2006	NDA Seq# 0007	Response to Clinical Comments dated March 15, 2006
23-Mar-2006	NDA Seq# 0006	Response to Microbiology Comments dated March 7, 2006; Resonse to Clinical Comments dated March 13, 2006; Response to Filing Communication Comments dated March 14, 2006
16-Mar-2006	Fax	Fax from FDA re clinical comments for -007 datasets
14-Mar-2006	Fax	Fax from FDA re Clinical Comments on 120-day Safety Update proposal sent February 24, 2006 SN 0002
9-Mar-2006	Fax	Fax from FDA (dated March 7, 2006 - not received until March 9, 2006) re Micro Comments sent to FDA dated February

		13, 2006
7-Mar-2006	Email	Re fax dated Feb 6, 2006 Clarification - status request
3-Mar-2006	NDA Seq# 0003	12-month Stability Update
27-Feb-2006	NDA Seq# 0004	Response to Microbiology Comments dated January 24, 2006 Submission of Resistance Report IDIX-06-101
24-Feb-2006	NDA Seq# 0002	120-Day safety update proposal
23-Feb-2006	NDA Seq# 0005	Response to Clinical Comments Fax dated February 6, 2006
13-Feb-2006	NDA Seq # 0001	Response to Microbiology Comments dated January 24, 2006; Submission of reports IDIX-05-114 and IDIX-05-115
8-Feb-2006	Email	Clarification required for Fax from FDA on Feb 6, 2006
6-Feb-2006	Fax	Clinical Comments re study day
27-Jan-2006	Mail	Letter re NDA Acknowledgement 22-011
24-Jan-2006	Fax	Fax from FDA re NDA 22-011 - Microbiology Comments
30-Dec-2005	NDA Seq# 0000	New Drug Application NDA No 022-011 - Sebivo (telbivudine) - eCTD on DVD-ROM